Emotional processing in mood disorder: clarifying the role of childhood trauma

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Emotional processing in mood disorder: clarifying the role of childhood trauma

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Abstract

Epidemiological studies suggest a high prevalence of depression in those who have experienced trauma and abuse in childhood. The aim of this thesis is to investigate the functional mechanisms of altered emotional processing that play a mediatory role in this causal relationship between childhood trauma and depression. From the perspectives of different scientific disciplines - psychophysiology, neuroendocrinology and behavioural psychology- emotional resilience and vulnerability to depression were investigated in order to consider different developmental pathways to psychopathology.

A total of 83 participants (29 male: 54 female) were recruited for this project. Emotional processing styles were concurrently examined using three different experimental measures, namely startle responses to emotional images (Experiment 1), cortisol responses to emotional images (Experiment 2), and facial emotion recognition (Experiment 3). These measures were undertaken in a cross-sectional study comprising four groups: healthy individuals with (N = 17) and without a history of childhood trauma (N = 24) and depressed patients with (N = 23) and without a history of childhood trauma (N = 19). All the experiments were conducted at the same day and with the same order (Experiment 3 follows Experiment 1) for each participant. During those experimental sessions saliva samples were collected to measure cortisol levels for Experiment 2.

Mediation analyses were conducted to examine possible roles of emotional processing styles examined in these experimental measures mediating the relationship between childhood trauma and depression.

Experiment 1) demonstrated strong normal affective startle modulation in healthy abused individuals contrasting with its absence in depressed individuals.
Experiment 2) demonstrated lower cortisol reactivity to emotional images in those with a history of abuse but no differences between healthy and depressed abused individuals.
Experiment 3) demonstrated more errors in recognising negative facial emotions but fewer errors on positive facial emotions within healthy abused individuals relative to healthy non-abused individuals. An opposite pattern of more errors in recognising

positive facial emotions but few errors on negative facial emotions was found within depressed abused individuals relative to depressed non-abused individuals.

The results from the mediation analyses found that suppressed startle amplitudes mediated the relationship between childhood trauma and depression and were a marker of vulnerability to depression, whereas the absence of this marker was associated with resilience to depression. However, the same analyses on cortisol reactivity and facial emotion recognition did not demonstrate significant mediation in the relationship between childhood trauma and depression.

The results of the study suggest that the retention of a normal affective startle modulation and the development of a positive bias in the recognition of facial emotions are implicated as functional mechanisms that render abused individuals resistant to depression. Reduced cortisol stress reactivity, that may reflect adrenocortical abnormality, was found in abused individuals.

The identification of these cognitive resilience factors that may be able to compensate for long-lasting effects of childhood trauma has important implications for the future design of the psychological treatments targeted specifically at the patient population with a history of childhood trauma.

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1.1. General introduction

1.1.1 Depression and childhood trauma

Depression is a common psychiatric disorder across societies; its symptoms have a detrimental effect on an individual's life and psychological condition. The symptoms comprise emotional deficits of inability to experience pleasure, hopelessness, helplessness and inappropriate guilt and regret, which pervade all aspects of life and disturb daily life activities and motivations. Approximately 17% of the population is said to suffer from this disorder and the symptoms are twice more likely to recur or to persist for life than to end just as a one-off episode (Kessler et al., 2003). The underlying causes of this persistent and recurrent characteristic of depressive symptoms have been investigated, including the connection with neurobiological and psychological mechanisms that underlie the development and maintenance of depression.

Childhood trauma is one of such factors whose impact endures into adulthood and that are considered to be causally associated with the subsequent manifestation of adult depression. A remarkably high proportion (approximately 25-35% depending on different definitions of trauma types) of depressed adults report experiences of childhood trauma (Kessler et al., 1997). Such individuals are also more likely to suffer from comorbidity (Kessler et al., 1997), chronic course of illness (Chapman et al., 2004; Wiersma et al., 2009) and multiple recurrent episodes in their lifetime (Nanni et al., 2012). In addition, their treatment outcome appears to be less favourable and their responses to a range of standard psychological and pharmacological therapies seem to be more complex than those of individuals without a history of childhood trauma (Harkness et al., 2012; Nemeroff et al., 2003).

This link between childhood trauma and adult depression suggests a strong and enduring impact of early life stress on the neurobiological and psychological mechanisms that underlie an individual's mental health, particularly at a stage of development where there is neuroplasticity. Changes occurring in these mechanisms due to early life stress seem to continue to affect individuals' mental health by

promoting a lifelong susceptibility to depression. Depressive episodes can manifest at multiple periods of adult life, not only occurring in temporal proximity to these early life stresses, but also with an interval of many years after the incidents of childhood trauma (Teicher et al., 2009)

1.1.2 Resilience and vulnerability

Despite being equally affected by childhood trauma, there are some individuals who do not manifest any psychiatric problems throughout their lifetime. Thus, whilst epidemiological studies demonstrate a high prevalence of depression within individuals with a history of childhood trauma, the rates are still only around a one in two ratio (Chapman et al., 2004), indicating that half of those individuals are somehow able to retain a healthy psychological state against the overwhelming risk of psychopathology. Specific neurobiological and psychological functions that may underlie such resilience to depression need to be considered. This resilience that protects individuals from psychiatric diagnoses is, then, a key to understanding the effect of childhood trauma on individual differences in the developmental pathways to depressive susceptibility.

Previous evidence suggests that a number of external factors may facilitate resilience. These include the psychosocial advantages of warm and stable psychological environments (Bradley et al., 2013), good parental and peer support, with secure attachment (Simeon et al., 2007b), and superior life quality from higher educational (Powers et al., 2009) or income levels (Campbell-Sills et al., 2009). Studies on those psychological and social supports indicate not just they help an individual to overcome the trauma but also act as a stress buffer to protect her from future stress-orientated psychiatric illnesses. Within an environment where positive views and self-appraisals of life are reinforced through harmonious family and peer relationships, one can gain psychological resources to enable good coping with adversity and that further facilitates successful adaptation to forthcoming stress later in life. With such positive external factors the individual may develop the capacity to manage her own stress levels with available social resources, and the impact of stress can be minimised including the possible detrimental outcome of a psychiatric condition. In fact, in addition to the potential benefits in future adulthood, positive aspects of family environment have also

been shown to contribute to resilience at the time the childhood trauma occurs (Bradley et al., 2013). Taking account of the social and psychological supports that can compensate the effects of early life stress is, therefore, crucial to explain individual differences in developmental pathways to resilience. However, it is also pointed that these external or objective factors should not be defined as equivalent to an individual's inner resilience, that is, the psychological and biological capacity that has been enhanced by actually facing stress, but not escaping away from stress. Environmental factors such as social supports are, indeed, powerful on their own to facilitate resilience. However, they do not directly explain resilience as they only ameliorate the impact of stress, but they do not represent internal factors that are established through stress exposure and that continuously affect an individual's way to respond to stress through life. Despite being strongly related to resilience, as shown in previous studies, objective environments also remain somewhat unreliable as a measure because subjective perception of environments does not necessarily match the objective perception of environments. For example, fostering may be considered as a positive environmental factor, but is not always successful in providing an individual with stable relationships with carers; thus,the same environment may affect different individuals differently in relation to their development of resilience. While the importance of psychosocial supports and their influences on developmental pathways to resilience are emphasised, it should also be noted that in terms of resilience, external factors are clearly differentiated from the functional ability to cope with stress and the capacity to resist psychiatric manifestations. In fact, researchers have argued that resilience should be explained by internal physiological and psychological coping processes rather than protective factors that are externally applied (Rutter, 2006). Resilience is considered as a "steeling effect" that emerges as individuals are repeatedly exposed to stress and are inoculated by highly stressful conditions. This "steeling effect" then increases their capacity to deal with future stressful situations and strengthens them to become resistant against the negative outcome of depression. Resilience with this definition should not be measured by external factors of given environments. Rutter (2006) suggests resilience should be measured by internal factors related to an individual's functioning and capacity that enables him or her to effectively cope with stress and thus prevent the manifestation of depressive symptoms. Previously this resilience was defined in multiple fields of research including genetics (Carli et al., 2011), neuroanatomy (Cisler et al., 2013), cognition (Geschwind et al., 2010; Wingo et al., 2010a) and behaviour

(Goldstein et al., 2013; Wingo et al., 2010b). It is of particular interest at the behavioural level. Subjective measures of effective coping strategies have been shown to moderate the severity of depression (Goldstein et al., 2013; Wingo et al., 2010b). Other studies using objective measures found that superior nonverbal memory (Wingo et al., 2010a) and greater positive affect (Geschwind et al., 2010), which may reflect effective emotional regulation, were associated with resilience to depression. Some personality traits such as extraversion and conscientiousness were found to be positively correlated to resilience (Campbell-Sills et al., 2006) Those studies are important to the extent that they inform us of a certain behavioural construct of resilience and its moderating effect on depression. However, previous research on resilience has been undertaken mainly using psychometric scales such as the Connor-Davidson Resilience Scale (Connor and Davidson, 2003) or The Resilience Scale for Adults (Friborg et al., 2003) as a measure of resilience. Thus it is still limited as it has not yet given insight into the functional mechanisms that underlie the identified resilience factors. Positive personality traits such as high self-esteem, optimism and emotional stability are also potential moderators for future psychiatric diagnoses and that may play an important role in promoting resilience. However, the mechanisms by which these factors influence resilience remains incompletely understood, and in particular their relation to other proposed resilience factors such as neuroendocrine or psychophysiological variables.

Resilience and vulnerability to depression as a function of childhood trauma are signified in two different population groups. These are healthy adults with a history of childhood trauma, which signifies their resilience to depression, and depressed adults with the same history, which signifies their vulnerability to depression. Investigating functional resilience and vulnerability is possible in a comparison of those groups within a cross-sectional design comparing groups of healthy and depressed adults with and without a history of childhood trauma. Previously, very few studies conformed to this sample strategy in order specifically to investigate factors associated with resilience and vulnerability. A number of endocrinological studies on childhood trauma and depression used a cross-sectional study design (Heim et al., 2000; Rao et al., 2008) and reported hormonal abnormality specific to the abused populations. However, they unfortunately did not analyse their results in light of hormonal resilience and vulnerability to depression by comparing directly the two abused sample groups of depressed and non-depressed individuals. As for behavioural research on the effect of

childhood trauma, there are a number of studies that have attempted to identify abnormalities in emotional processing, particularly in facial emotion processing, within children and adults who had experienced childhood trauma (Pollak, 2003). However, no studies have examined both healthy controls and depressed individuals with and without abuse. Therefore, it is not yet clarified how the identified emotional deficits specific to abused populations are related to susceptibility to depression.

The current PhD project will be the first attempt to identify such functional resilience and vulnerability to depression by conforming to the sample strategy explained above with a number of experimental measures examining individual differences of emotional responses to stress.

1.2: Review 1.

Facial emotion processing in maltreated children: A critical evaluation of current evidence and directions for future research

1.2.1. Introduction

Altered affective processing is hypothesised to mediate the link between early experiences of trauma and the adult psychopathology of depression. DSM-IV, The Diagnostic and Statistical Manual of Mental Disorders (First et al., 1995) specifies aspects of altered affective processing within the core symptomatology of Major Depressive Disorder (MDD). For example, deficient positive affect (e.g. anhedonia) and excessive negative affect (e.g. guilt, sadness) are terms that signify overall negative reactions towards emotional stimuli and are the most salient behavioural features of MDD. The clinical importance of understanding the nature of altered emotional reactivity has been recognised and a number of studies provide empirical evidence confirming fundamental alterations in the processing of emotional stimuli within MDD patients (Bylsma et al., 2008).

Epidemiological studies have also shown a high prevalence of depressive symptoms among individuals who have experienced childhood trauma (Chapman et al., 2004; Kessler et al., 1997; Wiersma et al., 2009). Thus, one suggestion is that the dysfunctional emotional reactivity inherent within the symptomatology of depression is acquired through exposure to an excessive amount of early life stresses or trauma, especially at key phases of psychological or neuronal development. A number of studies have directly examined the presence of such a relationship between early life stresses or trauma and altered processing of facial affect (Fries and Pollak, 2004; Pollak et al., 2000; Pollak and Kistler, 2002; Pollak and Sinha, 2002). These studies have indeed found aberrant facial emotion processing within the children with history of trauma, which raises the question as to whether this then represents a risk factor for the future development of depression, and whether this could represent a causal pathway linking childhood trauma and adult depression (Pollak, 2003).

The aims of this review is to summarise the body of published work linking altered processing of emotional facial expressions to childhood trauma, and critically evaluate whether such a link, if evident, could mediate the association between early experiences of trauma and adult vulnerability to psychopathology by analysing their experimental methodology and results.

Previous investigations of altered emotional processing have employed behavioural and psychophysiological measures to assess affective processing in maltreated children or in adults who have retrospectively reported the experiences of maltreatment. Behavioural tasks are used for probing deviation from normal processing styles inherent in those individuals' behaviours in response to socio-emotional stimuli. Psychophysiological measures of event-related-potentials (ERPs), skin conductance and heart deceleration have also been measured during exposure to the same stimuli. More recently, magnetoencephalography recordings have been used. I aim to evaluate such methodologies utilised to date and resultant findings, and identify how future studies might resolve the limitations of the existent studies and further advance this field of research.

This is a narrative review on previously published studies reporting the effect of childhood trauma on facial emotion processing. Relevant studies were identified by electronic searches of MEDLINE, PUBMED, and PsycINFO. References of the identified articles were also manually searched for the relevant publications. Key terms which were used for the electronic searches were: FACIAL EMOTION RECOGNITION, FACIAL EMOTION PROCESSING, and FACIAL EMOTION PERCEPTION. These terms were combined with the terms: CHILD (CHILDHOOD) ABUSE, CHILD (CHILDHOOD) MALTREATMENT, CHILD (CHILDHOOD) ADVERSITY, EARLY LIFE STRESS. Since I aim to specifically consider behavioural pathways from the events of childhood trauma to the development of depression, I exclusively evaluated behavioural and psychophysiological studies of facial emotion processing. Therefore, I did not undertake a comprehensive analysis of neuroimaging and genetic studies under the key search term.

1.2.2. Dysfunctional affective processing in depression

As described earlier, within the core of depression there are symptoms that represent behavioural deficits in affective processing or emotional reactivity. Two major theories have attempted to account for these emotional features of depression.

Firstly, Clark and Watson (1991) proposed a tripartite model contrasting the two major psychiatric syndromes of anxiety and depression and emphasised depression as a lack of

autonomic responsiveness as opposed to anxiety that is defined as physiological hyperarousal. In this model, anxiety and depression are fundamentally distinguished by the way an individual's physiological system responds, with depression uniquely defined by its attenuation of responsiveness of the system. Similarly, Rottenberg et al. (2005) proposed Emotion Context Insensitivity (ECI), suggesting that the low and dysphoric reactions in individuals with depression are caused by their impairment of flexibly adjusting themselves to changes in the emotional contexts of environments.

Both models are in line with previous experimental evidence on depression showing absence or little activity of the system in which normal individuals differently respond to the biphasic affective tone of positive and negative stimuli (Kaviani et al., 2004; Mneimne et al., 2008). They highlight a depressed individual's inflexibility in processing and responding to emotional information, in which the ability of unconsciously modulating responses differentially to the emotional content of stimuli appears to be compromised. The depressive symptom of pervasive anhedonia including a loss of interests or pleasures and a feeling of helplessness may develop from this rigid preconception and misconception in which an individual sees the world illusively as emotionally monotone and hopeless. Being unable to automatically process emotional information with more varied scope causes demotivation and leads to slowness and insensitivity towards any variation of emotional context. In other words, individuals whose automatic affective processing system is impaired are not capable of swiftly capturing positive emotional signals, resulting in them diverting their way of thinking towards atypically negative directions(Rottenberg et al., 2005).

1.2.3. The relationship between depression and childhood trauma: behavioural and neuroendocrinological research

The behavioural mechanism underlying this deficit of affective processing may be programmed at the developmental stage when the neural system is still plastic. Excessive stress from adverse and traumatic experiences in childhood may have a significant impact upon the process of shaping children's affective processing through such neuronal and neuroendocrinal systems (de Kloet et al., 2005). Such effects could then endure into adulthood, thus altering affective processing upon the exposure to another stressor encountered later in life, and consequently triggering the manifestation

of psychiatric disorders (Lupien et al., 2009). Evidence in the field of neuroendocrinology with respect to the effect of childhood adversity has recently been accumulated (Heim et al., 2008b), with the suggestion that a maladaptive hormonal system acquired in childhood may be responsible for the later development of psychiatric disorders. However, how the behavioural consequences of early life stress give rise to adult psychopathology has not yet been clearly defined. Indeed, some emotional deficits have been identified, particularly in physically abused children, and this has been assumed to be an early sign of symptomatology (Pollak, 2003), but this assumption has not yet been empirically tested. In order to verify such behavioural pathway to depression, viewing its pathogenesis from the two-point time frame of an early causal history and later clinical outcome is necessary in either longitudinal or retrospective studies. Very few behavioural studies have attempted to comply with such study design to date and most of the existing studies focus on probing an adverse behavioural outcome at a single developmental time point where children are still not known to be susceptible to future psychopathology.

Perceiving and recognising emotional signals from others is an important cognitive skill to survive many psychosocial environments. Incompetence in this skill of affective processing may cause dysfunctional interactions with peers and families. Consequent difficulties in interpersonal communication may result in an excessive degree of conflict and stress that, in turn, makes individuals more vulnerable to depression than individuals who have undergone the normal development of affective processing (Dodge et al., 1995; Repetti et al., 2002). Furthermore, emotional reactivity of negative affect deriving from a biased emotional perception may have the effect of diminishing the confidence that could normally allow them to manage a stressful event, and this discouraging effect causes further pathological stress reactions, including within their hormonal systems (Pedrelli et al., 2008).

Emotional reaction is facilitated by a multilevel system comprising both conscious and unconscious processing, which are complexly integrated to perceive and analyse emotionally coloured sensory inputs. Humans are already equipped at birth with a rudimentary system to process emotional stimuli so that they can begin to explore their first psychosocial environments, such as caregivers' signals (Black, 1998). However, newborn babies' perception is undoubtedly primitive and basic; therefore, they require a

long learning period until they finally gain a fully functional emotional system. Development of affective processing is experience dependent and highly variable, although it is also to a certain degree genetically determined (Ehlis et al., 2011). Any extreme environmental and psychological hazards causing atypical stress reactions are therefore potentially damaging to the process of normal development of affective processing, and can interfere with neuronal and neuroendocrine systems associated with its successful development.

Childhood trauma is considered one such threat to hormonal and behavioural development. Physical and sexual assaults, a lack of emotional bonds and poor parental care are assumed to cause an atypical amount of stress in children who only have a limited psychological and cognitive capacity to cope with such events and situations. Childhood trauma that takes place while synaptic pruning is actively ongoing can thus be a powerful adverse force to induce changes in neuronal and hormonal stress reactivity, which is one of the primary risk factors mediating development of depression (Young, 2004).

A number of neuroendocrine studies have been undertaken to investigate whether the experience of early life stress leads to alterations in hormonal states and in individuals' responses to additional stresses later in life (Carpenter et al., 2007; Carpenter et al., 2010; Heim et al., 2000; Heim et al., 2002) They suggest a certain neuroendocrine dysfunction as a consequence of childhood trauma that may underlie adult vulnerability to depression.

Behavioural studies on early life stress and its association with adult psychopathology, on the other hand, remain incoherent. In the following chapters, studies of the effect of childhood trauma on facial emotion processing, one of fundamental cognitive behaviours, will be summarised (Table 1.2.1) and analysed.

Table 1.2.1. Studies of the effect of childhood trauma on facial emotion processing

Reference	Sample type	Sample size	Tasks	Measures	Main findings
Pollak et al (1997)	7.1-11.4 years old	23 maltreated, 21 non-maltreated	Visual odd ball task + ERP	BM + PM	Maltreated children have shown larger P3b amplitude when responding to angry targets than happy targets.
Pollak et al (2000)	3-5 years old	16 physically neglected, physically abused, 17 non-maltreated	Emotion situation task + Facial emotion discrimination task	BM	Physically abused children have shown worse performances on recognising emotions than non-maltreated except for anger. Physically neglected children have shown overall poor performances.
Pollak et al (2001)	6-12 years old	28 maltreated, 14 non-maltreated	Visual oddball selection task + ERP	BM + PM	Maltreated children have shown larger P3b amplitude when responding to angry faces than non-maltreated.
Pollak & Kisler (2002)	Children with the mean age of 9.3 years old	23 physically abused, 17 non-abused	Facial emotion recognition task using continuous presentation between two emotional valences.	BM	Physically abused children have superior performances on angry faces.
Pollak & Sinha (2002)	8-10 years old	24 physically abused, 23 non-abused	Facial emotion recognition task using stimuli degradation	BM	Physically abused children were faster to identify anger than controls.
Pollak & Tolley-Schell (2003)	8-11 years old	14 physically abused, 14 non-abused	Posner task + ERP	BM+PM	Physically abused children have shown larger P3b amplitude on invalid angry trials than non-abused.
Fries & Pollak (2004)	Children with the mean age of 4.4 years old	18 postinstitutionalised adopted children, 21 controls	Emotion situation task + Facial emotion recognition task	BM	Postinstitutional children performed worse than controls in labelling all emotional situations with corresponding facial emotions except for anger.
Pine et al. (2005)	7-13 years old	34 maltreated, 21 non-maltreated	Dot-probe task	BM	Physical abused children tended to direct attention away from angry faces.
Shackman & Pollak (2005)	7-12 years old	33 physically abused, 30 non-abused	Emotion recognition task on the combination of both familiar and unfamiliar faces and voices	BM	Maltreated children have shown superior performances on vocal anger by their mother.
Cicchetti & Curtis	2.4-3 years old	35 maltreated, 24 non-maltreated	Passive facial emotion viewing + ERP	PM	Maltreated children have shown larger P260 amplitude when viewing angry faces than non-maltreated.
Shackman, Shackman & Pollak (2007)	7-12 years old	16 physically abused, 14 non-abused	Odd ball emotion recognition task + ERP + SC	BM + PM	Physically abused children have shown larger N2 amplitude when responding to irrelevant vocal anger than controls.
Masten et al. (2008)	8-15 years old with and without PTSD	29 maltreated, 17 non-maltreated	Facial emotion recognition task	BM	Maltreated children faster recognised all emotions than non-maltreated.
Pollak et al (2009)	9 years old	49 physically abused, 46 non-abused	Facial emotion recognition task, using photographic sequence between two emotional valences	BM	Physically abused children identify anger earlier in the sequesnce than non-abused.
Leist & Dadds (2009)	16-18 years old	23 adulscents with various levels of maltreatments including emotional, physial abuse and neglect	Facial emotion recognition task	BM	Maltreatment was associated with superior recognition of fear and sadness.
Gibb, Schofield & Coles (2009)	Undergraduates	47 maltreated, 170 non-maltreated	Dot-probe task	BM	Maltreated youths have shown a stronger attentional bias towards angry faces.
Sullivan, Carmody, & Lewis (2010)	Preschooled with the mean age of 4 years old	15 neglected , 27 non-neglected	Facial emotion recognition task + Emotion situation task	BM	Neglect is associated with overall poor performances on the tasks.

BM = Behavioural measure, PM = Psychophysiological measure, ERP = Event-related potentials, SC = Skin conductance

1.2.4. Facial emotion processing studies with behavioural measures

If emotion is an unconscious psychological trigger for subsequent motor actions, the physiological or behavioural activities following emotional stimulations would be justified as a plausible measure to assess the states of emotion initiating those activities (Power, 2008). For example, efficiency in categorising emotional valence that facial expressions represent implies individual differences in sensitivity to a specific

emotional stimuli valence. Enhanced sensitivity to a certain valence may lead to an enhanced accuracy and speed in recognising that valence, whereas reduction in those parameters may reflect a relatively lower level of interest and diminished sensitivity towards that same valence. Since facial expressions are universal (Ekman et al., 1969) and their correct recognition is essential for psychosocial survival, they are undeniably one of the most useful and appropriate stimuli to represent inner emotional activities (Darwin, 1872). Thus, they are not just ecologically valid but are the most salient stimuli mirroring human emotions. Disturbance in recognition of such stimuli could be highly problematic in psychosocial development and this underscores the importance of investigations of face recognition in relation to early stressful experiences that are assumed to impose behavioural abnormality.

In behavioural research on the effect of childhood trauma, a number of studies have focused on children's facial emotion recognition ability to examine how effectively children can identify the emotional valence displayed in facial expressions. In those studies, images of prototyped emotional valence such as anger, happiness, fear and surprise in facial expressions are morphed and presented so that emotional valences are gradually degraded and transformed from one valence to the other. Subsequently, participants are asked to identify the emotional valence of facial expressions, with different degrees of difficulty dependent on the degree of manipulated image degradation. When performance of physically abused children and non-physically abused children was compared in this task, the former showed a biased perception towards angry facial expressions in which their speed and accuracy of categorising this particular expression was significantly superior to the latter (Pollak and Kistler, 2002). This bias was consistent when less visual information (Pollak and Sinha, 2002) or more naturalistic information of facial muscular movements than static face images were available (Pollak et al., 2009). These findings suggest that abused children have overall a lower threshold to perceive anger and that their mental representation of anger is comparatively broad, including even expressions that show little or no explicit anger. This bias also facilitated a faster response to the target stimulus when the target location was primed by angry facial expressions in a well-known Posner attention task (Pollak and Tolley-Schell, 2003; Posner, 1980). This increased attention to anger stimuli has been demonstrated when the different sensory modality of auditory stimuli is used, in that physically abused children have shown difficulty disengaging their attention from

vocal anger simultaneously presented with emotionally incongruent visual stimuli (Shackman et al., 2007). Further enhanced anger bias for a familiar stimulus of their own mother's voice or face compared to strangers' has also been shown (Shackman and Pollak, 2005). In addition to this anger bias, there are also some studies which report other changes in facial emotion processing in maltreated children. Accurate categorisation of sadness and fear (Leist and Dadds, 2009) and avoidance but not preferential processing of anger (Pine et al., 2005) by maltreated adolescents and children, respectively, have been found. However, these studies are not directly comparable to the studies by Pollak and his colleagues claiming anger bias in physically abused children since the maltreated samples in these other studies comprised several different trauma types and these trauma types were not separately analysed.

Pollak (2003) explains that the hypervigilance to angry facial expression in physically abused children may well be adaptive in order to protect children from physical threats with swift detection of hostility cues in their surroundings. Hostility is the most salient emotional cue to predict imminent danger for children who are always aware of threatening sources around them, such as parental violence. By acquiring the biased attention towards hostility signals, they would be able to efficiently prepare for coming threats by physically or psychologically avoiding or escaping from the sources. Conversely, this behaviour can be maladaptive in a different context where such vigilant behaviours are not required. As children acquire an enhanced accessibility of the emotion of anger in their mental representations, aggressive responses are readily brought to their mind as an instrument of resolution of interpersonal confrontations. Such overreactions towards little or no hostilities may provoke dysfunctional interactions that, in turn, cause conflicts and stresses that may lead to psychiatric conditions (Dodge et al., 1995; Repetti et al., 2002).

However, it is noted that the studies of facial emotion recognition are predominantly examined in the comparisons between physically abused children and matched controls; thus, it is unknown whether this hostility bias is applicable to other types of trauma. Very few studies address this limitation. Among them, Pollak et al. (2000) compared responses in a facial emotion recognition task between physically abused and another type of trauma, physically neglected children, and this study yielded differential responses for those trauma types. Physically neglected children showed overall

diminished responses regardless of valence, in which they have difficulties discriminating facial expressions to match them to the narrative situations describing the target emotional categories. Neglected children who have been institutionalised in early life also indiscriminately showed difficulties identifying emotions displayed in facial expressions compared to non-institutionalised matched controls, except for identification of angry facial expressions, which was comparable for the both samples (Fries and Pollak, 2004). Another study of neglected preschool children also suggests their lack of sensitivity to overall emotions by showing relatively poor performances on labelling facial expressions with semantic emotional contents (Sullivan et al., 2010). Such global emotion hyposensitivity in neglected children draws a stark contrast to selective hypersensitivity to anger in physically abused children. This contrast between the maltreatment types is rather puzzling unless these differential behavioural outcomes are mediated by differential developmental pathways, in which a particular type of maltreatment leads to a particular emotional bias, or indeed a different vulnerability to psychiatric disorder. However, such specificity in the association between trauma types and disorders has not been recognised (McMahon et al., 2003). In addition, abnormal hormonal reactivity to adulthood stress exposure has been shown consistently in those with a history of both trauma types (Carpenter et al., 2007). This uniform evidence for early life stress in general might suggest that the existence of developmental pathways diverging to unique behavioural and clinical outcomes for each trauma type is unlikely. Alternatively, the discrepancy in the effects between the different trauma types could be explained if behavioural abnormalities are expressed independently from neuroendocrine abnormalities. Therefore, the aforementioned affective processing style specific to physically abused children may not solely derive from the hormonal changes that occur regardless of the types of maltreatment.

1.2.5. Facial emotion processing studies with psychophysiological measures

Although there remain some difficulties in drawing a clear-cut interpretation of behavioural evidence, event related potentials (ERPs), which more directly reflect brain responses than behavioural measures, appear to further consolidate the evidence of an anger bias within physically abused children. ERPs are an index of central nervous system functioning and reflect the underlying cognitive process of discrete stimuli.

These are particularly useful for examining which aspects of attention may be affected by childhood trauma. For example, N1 and P1 are deflections that emerge at the earliest attentional time window and involve face recognition, but they appear too early to exhibit evidence of emotional discrimination. Similarly, early negative deflection, N2, emerges at a relatively early time window of 200-500 ms onset but this has been interpreted as a representation of involuntary attentional processing. P3b is another significant component that emerges in a later time window of 650-850ms onset and this represents more voluntary control of attentional resource allocation.

Several studies by Pollak and his colleagues (1997; 2001; 2003; Shackman et al., 2007) measured ERPs in combination with various cognitive tasks. A visual oddball task, in which children were instructed to detect a target facial emotion within a number of irrelevant expressions, showed significantly larger amplitudes of P3b to angry targets within maltreated children than within controls (Pollak et al., 1997; Pollak et al., 2001). However, these amplitudes to other emotional targets such as happy and fearful faces showed no difference between those samples. This enhanced P3b to anger stimuli fits neatly with the behavioural evidence in other studies of pronounced perceptual bias and increased attentional control towards hostility cues within physically abused children. In addition, this anger bias appears to emerge at multiple attentional stages in processing facial emotions. The Posner task, which was administered in the same study reviewed earlier, was combined with ERP analysis and also elicited a selective increase in P3b in addition to P1 to anger stimuli (Pollak and Tolley-Schell, 2003). In this task, the prime – e.g. an angry facial expression – appears either at the same location, or in the opposite location, to the target stimulus that follows and to which participants are instructed to respond. Response time to take attention away from the opposite prime location (invalid trial) or to bring attention to the target with assistance of the prime at the same location (valid trial) suggests how efficiently the prime is processed to either distract or enhance, respectively, the response to the target stimulus. Priming an invalid location with angry facial expression led to an enhanced P3b as well as P430s in physically abused children, suggesting they require an increased attentional effort to disengage from the anger prime. On the contrary, during a valid trial they showed a larger P1 reflecting preattentive processing at a very early attentional time window, suggesting an early attentional bias towards anger. Another study also reviewed earlier, which incorporated different sensory modalities of auditory stimuli in the design (Shackman et al., 2007),

demonstrated an enhanced N2 to vocal anger that is designed to distract children's attention to target facial stimuli. These results indicate that both involuntary and voluntary levels of control are affected in selective allocation of attentional resources to anger stimuli within physically abused children; however, which level is affected seems to depend on the task requirements. Consistent with the behavioural results, such enhanced brain activities upon presentation of anger stimuli overall support physically abused children's selective sensitivity towards hostility cues.

Evidence from skin conductance and heart deceleration tests may augment those from the ERP studies, although the results are rather sparse compared to the well-established ERP and behavioural paradigms. Heart decelerations reflect an individual's strong orientation of attention to significant or new information. This was observed in physically abused children listening to background anger-related conversations while they engaged in a simple attention task that did not involve emotional regulation. However, a skin conductance test did not find arousal associations with anger tone in conversations in physically abused children (Pollak et al., 2005). Although another study found increased skin conductance responses to anger stimuli, and the magnitude of these responses were positively correlated with P3b and N2 amplitude (Shackman et al., 2007), associations between a biased attention and increased arousal still remain inconclusive due to the small number of studies conducted in relation to the effect of childhood trauma.

1.2.6. Discussion: Critical evaluation of the previous literature regarding facial emotion processing

An attentional bias to a hostility cue appears to be a consistently found behavioural phenomenon in the research on the effect of childhood trauma, and has been demonstrated both in behavioural and psychophysiological experimental paradigms. However, whether this phenomenon is solely applicable to children with the one type of trauma (physical abuse) or can be generalised to those with other trauma types remains to be answered. Pollak et al (2001) included a sample with a history of another trauma type, physical neglect, in addition to physical abuse in a number of their studies. They have shown an enhanced P3b to anger stimuli within this mixed sample of children,

which is consistent with other studies using a single sample of physically abused children compared with controls. However, since the behavioural results from the same sample showed different responses between trauma types (i.e. anger bias for physically abused children, diminished responses to all emotional valence for physically neglected children (Pollak et al., 2000)), this ERP evidence from the mixed sample is rather unconvincing. The authors did not report P3b results for the different types of trauma; thus, whether the P3b varies by trauma type in a similar fashion to the behavioural results is not known. It may be that behavioural results do not necessarily correspond to the results from psychophysiological measures. However, it would still be worthwhile teasing out the effects of trauma types on the ERPs to examine whether the anger bias is a general phenomenon across heterogeneous samples with a variety of types of early life stress or is completely restricted to physically abused children as their unique behavioural style.

Of note, several studies included a variety of trauma types as an integrated sample but most of them are unfortunately not comparable to the studies that showed the anger bias in physically abused children due to their use of different age groups. One ERP study found differences in the topographical distribution of various brain electrical activities between maltreated and non-maltreated infants (Cicchetti and Curtis, 2005) and a cognitive task of facial emotion recognition demonstrated an angry bias in young adults with a history of different trauma types (Gibb et al., 2009). However, the series of studies suggesting the anger bias mainly tested school-aged samples. Those studies using different samples of infants and adolescents are unlikely to support the evidence of the anger bias because both the timing of testing and the timing of traumatic incidents vary in all those studies. Developmental stages induce differential neuronal reactions to the same emotional stimuli; therefore, a comparative analysis of cognitive performance should not theoretically be made between different age groups. Interestingly, one other study did look at a similar aged group of subjects – i.e. school aged children – with a history of varied maltreatment types and found a global, but not anger-specific, emotion hypersensitivity (Masten et al., 2008).

Difficulties with these previous behavioural and psychophysiological studies remain in their tendency to conceptualise the effect of early life stress as a uniform concept, rather than as separate effects mediated by differential developmental pathways for trauma

types. In addition, whether the perceptive bias in physically abused children has a relatively short-term effect or continues to affect their adulthood behaviours by playing a role in pathogenesis of psychiatric disorders has not been fully investigated. A lack of evidence tracing forward their behavioural styles in adulthood makes this conclusion difficult.

One study by Weber et al (2009) using magnetoencephalography (MEG) attempted to address these problems by undertaking a retrospective study of adults who reported childhood trauma experiences. They conducted a study on a heterogeneous patient population, with diagnoses including schizophrenia, borderline personality disorder, post-traumatic stress disorder (PTSD) and depression, which had early experiences of various types of childhood maltreatment and stress. In this study, while the participants passively view pictures of a variety of emotional valences, brain responses were measured. Reduced early negative activities in posterior regions were found in the patients with depression. These responses were not specific to a particular valence but the normal enhancement in activities for positive and negative valence relative to neutral valence appeared to be attenuated in this sample. Early life stress was also negatively correlated with the magnitude of responses. However, an analysis of its interaction with diagnosis was not made. These samples were followed up at eight month after the initial study and, at the later time point, reduced cortical responses for the group of participants with intense traumatic experiences compared to those with less intense experiences was found (Matz et al., 2010). This reduced response in the maltreated population was significant independently from current diagnosis and current ongoing stress levels.

Evidence from the MEG study indicates that the effect of early life stress is stable over time and could be long-lasting, given that the deviation from the normal cortical response still continues to manifest in adulthood as a possible trait marker for adult psychopathology. Such studies make it possible to assess the causal link between early experiences of trauma and the later manifestation of psychiatric disorders. However, the patient samples in those two studies had a high diagnostic variability in a small sample size. Therefore, unfortunately, their statistical power is not sufficient to conclude whether there is any link between the identified abnormality in cortical responses and a particular disorder such as depression. Moreover, the follow-up study found no

evidence for a mediatory role of psychophysiological abnormalities between the experiences of childhood trauma and current diagnoses (Matz, Junghofer et al. 2010). Thus, there remains insufficient evidence of an explicit link between, on one hand, altered behavioural and hormonal functions as a consequence of childhood maltreatment experiences, and, on the other hand, later enhanced adult stress reactivity rendering individuals vulnerable to MDD.

1.2.7. Future recommendations

In summary, previous behavioural and psychophysiological studies suggest some key aspects in the dysfunctional development of facial emotion processing in children and adults who reported early experiences of trauma.

1) Behavioural studies examining efficiency in recognising facial affect indicate maltreated children have a pronounced bias to angry expressions and this affects multiple levels of attentional processing.

2) Psychophysiological results confirm behavioural evidence of this anger bias in maltreated children by showing deviation from the normal cortical responses upon presentation of angry expressions.

However, a number of concerns regarding those conclusions are to be raised. Firstly, a sample selection bias should be removed to determine whether the anger bias is present equally in samples with histories of a variety of trauma types. Ideally, a separate effect of each type of childhood trauma (i.e. physical abuse, sexual abuse, emotional abuse, neglect, and general traumatic experiences) should be additionally analysed as they may have differential effects on the development of facial emotion processing. Secondly, to verify the assumption of causality between childhood trauma experiences and adult-onset psychiatric disorders, studies should be conducted at two time points including both the causal point and outcome point. Since a prolonged effect of childhood trauma is postulated (Lupien et al., 2009), whether the deviation from the normal behavioural function continues to be observed through the course of life, and the degree to which this continues to affect individuals' psychological wellbeing, is of great interest. Thirdly,

behavioural abnormalities should also be understood within the framework of brain biology, with the identification of any links to other markers such as altered hormonal systems that have been linked to the adult onset of depression (Burke et al., 2005).

Indeed, identification of this "brain-behaviour" relationship is extremely challenging particularly because affective processing itself is such a complex set of mental processes that are difficult to be fully biologically conceptualised. In recent decades, the neuroanatomical involvement of the amygdala has been conjectured as a central mechanism generating one of the central emotional constructs described in this review, i.e. fear (LeDoux, 1996). However, the amygdala response may account only for one of a set of complexly interrelated sub-processes that compose an emotional reaction. Captured emotional sensory input is firstly acknowledged, then decoded, understood in the applied context, and further interpreted and analysed in ones mental representation of emotional repertoires in order to give rise to a suitable action to the current emotional context. Multiple levels of processes are postulated in this seemingly seamless but actually very complex and manifold operation. It remains a challenge to link specific biological changes such as amygdala dysfunction or elements of the HPA axis response to specific components of affective processing of facial expressions.

In order to address the concerns raised above, the following theoretical and methodological improvements are recommended for the future research on altered facial emotion processing mediating between childhood trauma and adult psychopathology. Firstly, different trauma types should be separately analysed so that the facial emotion processing style specific to each trauma type is identified and how each of them can lead to the different symptoms of psychiatric disorders is verified. Secondly, a longitudinal study should be conducted to trace forward the effect of childhood trauma to examine how the initially identified emotional deficit results in a later manifestation of depression. Thirdly, the research should be viewed from the perspective of 'brain-behaviour' relationship and an integrative methodology of biology and psychology, such as a simultaneous examination of behavioural and biological responses to the same condition, should be explored. Finally, when examining the developmental outcome, a cross sectional study using a variety of samples such as healthy controls and depressed patients with and without the experiences of childhood trauma should be conducted, to see whether depression following on from early life stress has a different psychological

or biological signature to that unrelated to early life stress. This sampling strategy would also make it possible to identify individual differences in the response to early life stress. For example, it would be possible to identify factors differentiating those who develop vulnerability to depression in comparison to those who develop resilience despite similar degrees of exposure to early life stress.

1.3. Review 2:

The effect of childhood trauma on hormonal stress reactivity: adaptive regulation that confers resilience and vulnerability to depression

1.3.1. Introduction

Stressful life experiences often precipitate the onset of depressive episodes; indeed, the majority of depressive episodes follow a major life event (Lloyd, 1980). Consequently, dysfunctional stress reactivity is a fundamental factor predisposing the development of depressive disorders (Burke et al., 2005). The functional mechanism of neural stress reactivity is via a cascade of interrelated neural activities involved in the sympathetic nervous system as well as the neuroendocrine system of the HPA axis (hypothalamic-pituitary-adrenal axis). In depressed individuals, the complex orchestration of these neural activities seems to be disrupted in characteristic patterns (Young, 2004).

At exposure to an acute stress, various neural activities are initiated from the brainstem region of the locus ceruleus releasing noradrenalin that acts on human physiological and behavioral capacities. This sympathetic activation is to enhance bodily energy mobilisation and emotional vigilance and arousal that are essential for effectively tackling the threatening situation. A chain reaction of the stress hormones in the HPA axis then follows to support the homeostasis of neurochemical balance. This stabilises the neural activities and eventually terminates all the stress responsive activations at the end of the stress condition. It is known that this HPA activation has a strong influence on cognitive and emotional functions, which seems to be compromised in depressed individuals. In particular, an atypical HPA hyperactivity is well-known as a major neurophysiological phenomenon of depressive psychopathology (Holsboer, 2001; Nestler et al., 2002; Young, 2004). A functional state that is liable to express abnormal HPA hyperactivity is thus believed to be one of the main biological components contributing to an individual's vulnerability to mood disorders.

However, how an individual gains this hormonal vulnerability to depression is not yet fully understood. Vulnerability may be determined environmentally, genetically or by the interaction of both. Recently, a number of genes that are associated with the development of depression when combined with stressful life experiences have been identified (Caspi et al., 2003; Ritchie et al., 2009). However, a history of traumatic

experiences in the early environment, such as parental abuse and neglect leading to atypical stress in children is still, on its own, considered to be a major source of vulnerability to depression. Early stress may have a strong impact on the regulation of individuals' hormonal functionality during a period of neural plasticity. The hormonal functional state of reactivity determined by this early stress reaction might potentially continue to affect their psychological and psychiatric conditions throughout their lives. There has been some research to date into this effect of early life stress in the field of neuroendocrinology. This research has offered substantial evidence of altered hormonal stress reactivity in youths and adults associated with a childhood history of traumatic experiences, suggesting a possible mediatory role in the subsequent risk of later depressive illness.

1.3.2. Aim

The aim of this review is to summarise the evidence concerning the neuroendocrine effects of early life stress, and consequent vulnerability to psychopathology such as PTSD and depression due to a dysfunctional response to other stresses encountered later in life. However, previous evidence on this effect is somewhat contradictory due to inconsistencies in ages and gender of samples, participants' ongoing psychiatric conditions and experimental methodologies. In this review, an attempt is made to disentangle these factors. Subsequently, a challenge will be made to theorise a model on hormonal vulnerability to depression as a function of childhood trauma by gathering and analysing the implications from the previous evidence. Aiming specifically to examine hormonal stress reactivity rather than simply looking at hormonal levels per se, the present review will exclusively refer to the studies on stress responses to laboratory psychological challenges. It will therefore not include comprehensive examinations of previous studies focusing on basal and diurnal hormonal levels of HPA axis hormones in non-stress reaction paradigms. The general limitations of previous studies on hormonal stress reactivity in association with childhood trauma will also be discussed. Subsequently, a proposal for more instrumental and effective methodologies will be made by suggesting an alternative view for this particular research question regarding the relationship between childhood trauma and psychopathology mediated by altered hormonal stress reactivity.

1.3.3. The HPA axis and stress challenges

As a person confronts a stress-provoking situation, a coordinated physiological response is immediately activated through the brain and body so that he/she can efficiently prepare for the subsequent actions to fight or escape from this emotional threat (Cannon, 1932). A key system of this stress response is neuroendocrine via the HPA axis involving a chain reaction of a number of stress hormones synthesised in and released from various neuroendocrinal regions. Following the perception of an adverse stimulus, a sequence of hormonal activity is initiated from the paraventricular hypothalamus by secreting and releasing CRH (Corticotrophin-releasing-hormone). CRH then stimulates the anterior pituitary to secrete and release ACTH (adrenocorticotropic-hormone), which travels through peripheral circulation to the adrenal cortex. In response to this ACTH stimulation, the adrenal cortex secretes and releases the glucocorticoid cortisol which acts on two types of receptors, MR (Mineralcorticoid Receptor) and GR (Glucocorticoid Receptor) that are ubiquitous in the limbic regions including the hippocampus, the hypothalamus, the amygdala and other brain and peripheral regions. This cortisol stimulation in turn provides negative feedback, suppressing CRH release at the hypothalamic level and ACTH release at the pituitary level, thus regulating the entire HPA homeostatic loop.

The HPA circuitry of these stress hormones has differential effects on cognitive and emotional functions depending on the duration and intensity of the stress. The HPA stress reaction can initially be beneficial to those functions that protect against threats by producing an emotional alert of increased attention to danger and enhancing memory function to associatively remember the emotion of fear with the given threatening situation. However, this can become detrimental when it is chronically activated (McEwen, 2003). The anatomical and functional correlates of such adverse stress reactivity, and which are likely to cause the development of a psychopathology, are found in a number of brain regions. For example, the hippocampus is particularly vulnerable to the toxic effect of excess of cortisol resulting from chronic HPA activation. A loss of volume in the hippocampus that is suggestive of memory impairment has been found in both clinical and healthy samples following exposure to a long period of

traumatic experiences (McEwen, 1999). Hyperactivity of CRH release is associated with an atypical emotional response of heightened fear, as shown by the enhanced startle and freezing induced by exogenous CRH treatments in animal studies (Koob et al., 1993; Liang et al., 1992). Cortisol hyperactivity is associated with anxiety through enhanced positive feedback at the level of the amygdala, which, in turn, increases CRH responses (Roozendaal et al., 2008).

The negative emotions of fear and anxiety generated by chronic HPA activations are a key feature in the symptomatology of anxiety and mood disorders, implying a causal link between chronic HPA activation and those symptoms (Burke et al., 2005). Childhood trauma, by causing excessive stress and generating HPA activation, could be one of the primary sources facilitating this dysfunctional stress reactivity, thereby leading to a later manifestation of psychiatric symptoms.

A number of methodologies are used to examine this HPA activity with different target hormones. As a contrast to diurnal activity demonstrated in the hormonal pattern of fluctuations over time in a day, reactivity is assessed by the peak increases of hormones in response to psychological and physiological challenges. Cortisol as well as ACTH and CRH concentrations are measured in different biological specimens - i.e. serum, plasma and saliva – in order to examine this reactivity. One of the common methods for this examination is the DST (Dexamethasone Suppression Test); this test measures the level of endogenous production of cortisol and specifically the extent to which there is hypersecretion of cortisol and/or resistance to negative feedback. (Newport et al., 2004; Stein et al., 1997). However, this pharmacological approach is criticised for its failure to examine naturally occurring stress activity and because dexamethasone does not provide sufficient information about central CRH drive or MR/GR receptors due to it not passing through the blood brain barrier (Meijer et al., 1998; Rao et al., 2008).

The psychological challenge paradigm is also frequently used to identify the nature of hormonal dysregulations by comparing the stress activations between the target sample and controls. Evidence of hormonal stress reactivity to psychological challenges in relation to different psychopathology is summarised below. It will become clear that, whilst previous evidence does indicate altered stress reactivity in general in individuals with a history of childhood trauma, there are significant discrepancies in the results seen,

including in the direction of change of stress reactivity. Methodological issues that may explain this inconsistency in the previous evidence will co considered and discussed.

1.3.4. Depression

Heim et al's study (2000) compared stress reactivity between depressed and healthy women with and without a history of childhood trauma. As in other similar studies, they used a standardised psychosocial stress challenge the TSST (Trier Social Stress Task (Kirschbaum et al., 1993) in which the participants are asked to perform speech and mental arithmetic tests in front of feigned judges. In response to this stress challenge, both ACTH and cortisol were found to have increased significantly more in depressed individuals with a history of childhood trauma than those without. In addition, cortisol was found to have increased more in women with a history of childhood trauma when they were depressed than when they were not. A regression analysis on the same sample found both peak ACTH and cortisol responses were predicted by a history of childhood trauma and by severity of depression, and this stress reactivity was further enhanced when additional trauma in adulthood was experienced (Heim et al., 2002). Using the same stress challenge, cortisol was also significantly increased in depressed adolescents with a history of childhood trauma compared to those without, but only when their symptoms are mild (Harkness et al., 2010) or when combined with additional adolescent stress (Rao et al., 2008)

1.3.5. PTSD

Several PTSD studies have used alternative methods to the TSST as a psychological challenge. As one of such, the method of exposure to traumatic scripts induced greater cortisol increases in female PTSD patients with a history of childhood trauma than healthy controls with the same history (Elzinga et al., 2003). However, a study using the cognitive and emotional demands of the emotional Stroop test as a stress did not demonstrate differences in cortisol reactivity between healthy controls and PTSD patients with a history of sexual abuse (Klumpers et al., 2004). Similarly, a study using

the TSST did not find differences in cortisol responses between abused PTSD patients and healthy non-abused controls (Bremner et al., 2003).

1.3.6. Healthy individuals

Studies using healthy adults mainly show a blunted HPA reactivity in those with a history of childhood trauma. It was found that the peak response of both cortisol and ACTH to TSST challenge was lower in those adults with a history of childhood trauma than those without (Carpenter et al., 2007; Elzinga et al., 2008) and that this is particularly significant in women with a history of a specific type of trauma -- physical abuse (Carpenter et al., 2010). One study using a simultaneous administration of both pharmacological (CRH) and psychological (TSST) challenges on healthy adults lead to an increased HPA reactivity in men, but not in women in association with the severity of childhood trauma (DeSantis et al., 2011). A blunted cortisol reactivity to the TSST has been also shown in healthy abused children at the age of 12 years old (Ouellet-Morin et al., 2011) or older (MacMillan et al., 2009). However, when another psychological challenge was used, in which subjects viewed violent pictures, enhanced but not blunted cortisol reactivity was found in healthy aggressive children with a history of physical fighting in schools as well as with a history of childhood trauma (Ivanov et al., 2011).

1.3.7. Sample comparisons

There is an obvious discrepancy between the two opposite findings – hyper- and hypo-reactivity of the HPA axis – in previous studies. However, it may be possible to integrate the findings from an alternative viewpoint. Rather than seeking to understand the findings exclusively in terms of adverse effects or vulnerability, viewing the results also from the perspective of resilience may help explain the differing findings to date, and why individuals who have suffered childhood trauma may respond in opposing ways.

From the fact that not all individuals who have a history of childhood trauma become clinically depressed, it is reasonable to assume that there is a certain vulnerability factor

which only affects those who go on to experience depression as adults. Resilience, in contrast to this vulnerability, is expressed in the individuals who continue to be healthy despite the adversity experienced in their childhood. This resilience factor enables individuals to effectively adapt to the given adverse childhood environments and supplies them strength to resist stressors experienced later in life.

The healthy sample used in the above studies is an example of this successful adaptation to the hormonal disruptions experienced during childhood trauma. Their blunted cortisol and ACTH responses imply a possible downregulation that occurs at the pituitary and adrenal levels in response to atypically increased activations of the HPA axis. This is a counterregulative adaptation, which subsequently affects future hormonal stress reactivity by reducing the HPA responses to another stressor. Failure to facilitate this downregulation may, therefore, reduce an individual's capacity to effectively regulate the HPA responses, thus rendering him/her more likely to manifest depression. Adrenal downregulation is particularly indicative of this adaptation as it has been demonstrated that cortisol reactivity in healthy adults with a history of childhood trauma was significantly lower than in depressed adults with the same history (Heim et al., 2000).

Other evidence, however, suggests that the experiences of childhood trauma could also sensitise the HPA axis in some individuals. This occurs to those who are not able to develop the above physiological resilience that prevents the later HPA hyperactivity. As mentioned earlier, generally in depressed individuals, hormonal stress reactivity is enhanced relative to non-depressed individuals (Holsboer, 2001; Nestler et al., 2002; Young, 2004), suggesting hormonal hyperreactivity to stress is causally associated with depression. This enhanced hormonal stress reactivity, however, seems to be more pronounced in those who have experienced childhood trauma than those who have not (Heim et al., 2000; Heim et al., 2002). This indicates that childhood trauma may amplify the HPA responses to stress for some individuals, which further increases the likelihood of developing depression. Thus, instead of gaining strength to resist stressors, this theory suggests that individuals acquire excessive sensitivity of neuroendocrinal regions to stress, which renders them more vulnerable to depression than those who have not developed the same sensitivity. This mechanism of sensitisation in relation to an individual's vulnerability to depression is in sharp contrast to that of the adaptation to early life stress described earlier, which provides resilience to prevent hyperreactions

to stress in other individuals who remain free from psychiatric disorder through their life span.

In addition to the environmental factor of childhood trauma, innate or early acquired neuroendocrine sensitivity is considered to play a role in shaping vulnerability and resilience to depression. Predisposition is thus a crucial factor that divides individuals' developmental pathways into two opposite directions, towards those vulnerable to, or resilient to, developing a psychiatric condition. Previous authors have described these diverging developmental pathways using the following functional mechanisms. The former represents "stress inoculation" in which an individual becomes increasingly tolerant of stressors by suppressing his/her own hormonal reactions (Elzinga et al., 2008). The latter explains a "priming" effect of repeated stress exposure that further enhances reactions to make an individual more susceptible to depression (De Bellis, 2001). It is not exactly yet known why and how individuals are differently affected by the experiences of childhood trauma in such a way that they express different susceptibility to depression. However, it seems likely that their neuroendocrine sensitivity is predetermined so that it guides individuals through to the two opposite developmental outcome by interacting with various environmental inputs including experiences of childhood trauma.

Genetic variation or pre- or post-natal experiences are likely candidates for the factors determining whether neuroendocrine regions are liable to be counterregulated (downregulated) or sensitised (upregulated) in response to early life stress. Two models describing this physiological capacity in relation to the effect of childhood trauma are proposed. The first model postulates a dichotomy in which an individual is liable to undergo either an adaptive (resilience) or maladaptive (vulnerability) response to early hormonal aggression. The second model is explained in a variation of regulative thresholds which set a point dividing their hormonal states into either being vulnerable or resilient to depression depending on the intensity or duration of the early life stress. In this model, neuroendocrine regions are increasingly sensitised only when the stress level exceeds the threshold but would be under control as long as it is kept below the threshold.

These models need to be examined by a refined sampling methodology using both vulnerable and resilient populations to depression. A longitudinal prospective study measuring hormonal levels at different developmental points before and after the events of childhood trauma together with the developmental outcome of psychiatric conditions could test the hypotheses of the models. Probing dysfunctional hormonal stress reactivity prior to the occurrences of childhood trauma is here of the highest priority. It would help not just predict an individual's future susceptibility to depression but also implement early interventions depending on his/her status of hormonal stress reactivity.

A limitation of these models is also noted. The findings from different studies using either healthy or depressed samples are not, in a strict sense, comparable. Unless physiological capacity is examined by comparing the populations appropriately representing their resilience and vulnerability to depression in a single design, it is difficult to verify the interpretations of the previous evidence into these models. Unfortunately, Heim et al's studies (Heim et al., 2000; Heim et al., 2002) used only female adults whereas all other studies use both female and male adults (Carpenter et al., 2007; Carpenter et al., 2010; DeSantis et al., 2011; Elzinga et al., 2008). Thus those studies are crucially different with respect to the sampling strategy, which is to be avoided when multiple studies are connectively interpreted. Gender differences, as well as the female menstrual cycle and use of oral contraceptives, are all known to significantly affect hormonal stress reactivity (Kirschbaum et al., 1999). It is thus essential to control this gender effect in future studies if the above models are to be tested.

Indeed, it is still premature to conclude that it is a predetermined physiological capacity that plays a causal role for future susceptibility to depression by influencing sensitivity of the neuroendocrine region to atypically increased hormonal activations. However, the alternative interpretation suggested here is hoped to encourage a new approach to the role of childhood trauma in the development of depression. An approach which focuses not only on the consequences of early life stress but considers also the adaptive mechanism of hormonal regulation to early life stress would provide further understanding of the developmental outcome in terms of adulthood psychopathology.

1.3.8. Age

The above reviewed studies mainly used adult samples whose hormonal activities reliably show a consistent pattern in response to similar types of stress stimuli under similar laboratory conditions. At maturation of the relevant neural regions, their responses are no longer influenced by the developmental process, thus their hormonal activities in general are assumed to be relatively stable over time. Studies using adult samples have this advantage that permits an examination of a genuine effect of group differences, whereas studies using young samples may be systematically varied by the additional factor of developmental process. However, in order to identify what precisely is the adaptive mechanism of the HPA axis to early life stress, it is also necessary to understand how the system is regulated at the very moment at which children are experiencing ongoing adversity. Investigation of how the developmental process interacts with the adaptive mechanism to the effect of childhood trauma then would clarify individual differences of developmental pathways to psychopathology.

A number of studies have used young samples whose hormonal maturation was still in progress. The effect of neuroanatomical development as well as that of alterations in sex hormone levels at the pubertal stage, indeed, makes the picture of hormonal regulations appear much more complex (Simerly, 2005). Great caution thus should be applied to interpretations of the evidence demonstrated in studies using young samples.

One such study, a longitudinal study of the HPA axis of young individuals with a history of childhood trauma, has shown that an initial HPA hyperactivity is suppressed over time while children progress to adolescence (Trickett et al., 2010). However, at which time point or age period this transition from hyper-reactivity to hypo-reactivity is facilitated is not yet fully elucidated. In fact, previous evidence appears to be inconsistent partly because sample age ranges are not uniform in those experimental studies. Moreover, there still remain a number of important variables to be controlled, such as intensity, duration, the age onset of adversity, and the time that has passed from the onset of adversity until children are actually assessed in a study. These more detailed aspects of adversity should be taken into account in order to capture the whole

picture of the function of stress. Then, how each of them independently or interactively influences the process of hormonal regulation should be analysed together with the developmental outcome.

Previous studies have mainly used a psychological stress challenge (the TSST) on Adolescent samples with various age ranges, using either healthy or depressed individuals or both in comparison. In one such study, Harkness et al (2010) found an increased cortisol level in response to psychological stress challenge in depressed youths with a history of childhood trauma only when their depression remains at a mild/ moderate level. However, when the level of depression becomes more severe, both youth groups with and without a history of childhood trauma show the opposite direction of decreased cortisol responses. Increased cortisol responses in depressed youths were also strongly predicted by the combination of childhood trauma and chronic stress during their adolescences (Rao et al., 2008).

The enhanced hormonal stress reactivity in youths with a moderate level of depression and with a history of childhood trauma is in line with that in depressed adults, suggesting their excessive neuroendocrinal sensitivity to stress activations. However, Harkness et al's finding of decreased stress responses in a severe form of depression contradicts the theory of sensitisation in which depression should actually generate increased stress responses. This discrepancy in hormonal stress reactivity between different severities of depression in youths may be explained by considering their responses as part of an adaptive mechanism of hormonal regulations. As an individual endures stressful conditions such as chronic depressive symptoms, the HPA system may shift to a hypo-reactivity from an initial hyper-reactivity. This is probably the same adaptive mechanism of downregulation of neuroendocirinal regions proposed earlier. In this case, the symptoms themselves play a role generating chronic HPA activations similar to the role of childhood trauma causing a downregulation of the adrenal level. This is because youth depression is considered to affect the HPA axis functioning differently from adult depression as their hormonal stress reactivity is still under development and their hormonal regulation is an ongoing process. Stress stimuli such as the depressive symptoms are therefore likely to become a source contributing to adaptive mechanisms at this particular period of plasticity.

If a depressive episode in adulthood derives from the experience of childhood trauma, a certain time interval normally intervenes between the two incidents. It then would give a temporal space to allow the completion of the adaptive regulation to shape the HPA axis as a fully matured system. Adult depression is thus a consequence of, rather than the process of, hormonal dysregulation. Therefore, the sensitivity of neuroendocrine regions is supposed to be more or less fixed to react to various stress sources, as is observed in hyper-stress reactivity in depressed adults. However, in youths, hormonal regulations are an ongoing process and the HPA axis is not sufficiently matured to react to stress in the same way as in adults. This may render youths' stress reactivity still changeable. Even stress stimuli such as depressive symptoms may further influence the adaptive mechanism of hormonal regulations, promoting the transition from hyper- to hypo stress hormonal reactivity.

Overall, converging evidence suggests that at a certain point, an initial hyperreactivity shifts to hyporeactivity to stress activations during the course of development. However, an age period or a developmental stage at which it is likely to occur has not been yet specified. One study has shown that healthy children who were as young as 12 years old already seemed to have acquired hormonal stress hyporeactivity after having early adverse experiences (Ouellet-Morin et al., 2011). Another study using older healthy female youths (12-16 ages) has also shown decreased cortisol responses to stress challenge in those with a history of childhood trauma (MacMillan et al., 2009). This study, which controlled for the variable of menstrual cycle, suggests that puberty, which is likely to be considered as a set point of the transition, may not be the major factor causing the transition to hyporeactivity. In fact, the shift from hyper- to hypo- reactivity may occur at any point of development. Instead of having a critical time point for a hormonal change, development may offer a volatile hormonal state that is moulded by the form of stress such as intensity, duration and types of trauma. Future studies examining hormonal stress reactivity in developmental ages may therefore need to take such ongoing hormonal regulation in youths into account and include the analyses of different aspects of trauma to identify the total picture of hormonal adaptation.

1.3.9. Experimental methodologies

A majority of previous studies which examined hormonal stress reactivity in relation to childhood trauma have used the same experimental method of stress challenge: the TSST. This set of arithmetic tests and public speaking is designed to impose psychosocial stress on individuals and has been widely used for probing individual differences in hormonal reactions to stressful conditions. It has successfully identified hormonal stress reactivity specific to individuals with a history of childhood trauma and with diagnoses of such psychiatric disorders as depression (Heim et al., 2000; Rao et al., 2008), PTSD (Bremner et al., 2003), personality disorders (Simeon et al., 2007a) and anxiety disorders (Elzinga et al., 2010).

However, although the TSST seems fairly effective in imposing stress on a wide variety of populations, there still remains a limitation in which it may not always produce sufficient stress to result in increased hormonal activations. For example, it is evidently influenced by cognitive processing of perception in which each individual may consider the condition imposed by the test as different degrees of stress. Individuals who have psychiatric symptoms such as fear of performing a task in front of strangers may perceive the TSST condition as relatively severe stress whereas others may perceive it as stress at a much lesser degree (Dickerson and Kemeny, 2004). Anxious persons may have a significantly greater response for this type of stress challenge than others, whereas the TSST may not be as effective as a recall of personal traumatic experiences for individuals suffering from PTSD and depression. It is worth noting this experience-dependent and symptom-specific aspect of psychological stress when using those tests to expect to produce the corresponding hormonal stress activations.

Instead of the TSST, a number of studies have used different methods of psychological stress challenge on individuals with a history of childhood trauma. They include violent picture showing (Ivanov et al., 2011), emotional Stroop test (Klumpers et al., 2004) and exposure to scripts describing the traumatic events the participants have experienced (Elzinga et al., 2003). The emotional Stroop test did not appear to be sufficient to yield differences in hormonal reactivity in female PTSD patients with and without a history of sexual abuse, which is perhaps understandable for the relatively mild stress the test is capable to induce. However, other methods were more effective and have successfully demonstrated an increased hormonal response to their imposed stressful conditions in individuals with a history of childhood trauma compared with those without.

Particularly, the exposure to personally relevant scripts of childhood trauma had a strong effect of heightening the hormonal reactivity in female patients with PTSD. When compared with the relatively small effect of TSST on some psychiatric conditions, this suggests that the TSST is not necessarily the most useful or appropriate measure of hormonal stress reactivity in these patients. In a study of patients with PTSD, the TSST induced an increased hormonal response prior to the task administration, probably because of the anticipatory anxiety towards an unknown experience, but it did not while the patients were engaging in the actual task (Bremner et al., 2003). Similarly, exposure to a violent film that reflected the prior behaviour of aggressive children induced a greater increase in cortisol responses in those with a history of childhood trauma than those without (Ivanov et al., 2011). To date, personally relevant materials have not yet been used to examine hormonal stress reactivity in depressed individuals with a history of childhood trauma.

Although the TSST is considered a standard method for examining stress reactions in individuals with various psychological and psychiatric conditions, explorations of other methods of producing stress in a laboratorial condition are still needed. Tailored methodology accounting for the behavioural characteristics of the symptoms for a specific psychiatric condition may be advantageous to induce sufficient stress resulting in measurable hormonal activations. In the investigation of the role childhood trauma plays in the development of depression, particularly, material relevant to personal trauma may be useful in identifying the function of stress caused by childhood trauma leading to psychopathology.

1.3.10. Discussion

The inconsistencies in the previous studies of hormonal stress reactivity in individuals with a history of childhood trauma can be attributed to various factors confounding the experimental designs to systematically vary the results. In this review, the three factors of sample composition, age and experimental methodologies used for the previous studies have been reviewed, with an analysis of how those factors may influence the results and thus lead to the disparate conclusions. In addition, by disentangling those factors, this review has attempted to clarify the adaptive mechanism to early life stress,

which may play an important role in determining an individual's future susceptibility to depression. Accordingly, a number of conclusions can be drawn in relation to the association between each confounding factor and the individual differences in hormonal regulation in response to intense stress activations caused by childhood trauma.

1) Different sample-comparison strategies may generate two opposing conclusions about the direction of alterations in hormonal stress reactivity in adults with a history of childhood trauma. In terms of the neuroendocrine response, depressed adults show hyper- reactivity to stress whereas non-depressed adults show hypo-reactivity to stress, following the experience of childhood trauma. This may be because their HPA axes are regulated differently (down-regulated in non-depressed adults but up-regulated in depressed adults) depending on their neuroendocine sensitivity to chronic hormonal activations. Two models – the dichotomy model and the regulative threshold model – determining an individual's future susceptibility to depression are proposed. However, this interpretation of the previous evidence is still tentative and needs to be verified in refined sample comparisons using populations appropriately representing vulnerability and resilience to depression.

2) Developmental processes are a factor likely to produce inconsistencies particularly when age ranges are not controlled. Developmental stage can also affect the ongoing hormonal regulation in response to current adversity in children, complicating interpretations of results. During development, hypo-reactivity is suggested to follow an initial hyper-reactivity to such intense stress exposure as childhood trauma and depressive symptoms. Previous studies suggest this transition may occur at any time frame of development from childhood to adolescence. Thus, developmental process may not offer a particular time point or window for the changes in hormonal stress reactivity but leaves the hormonal state to respond to early life stress in a more volatile manner. In addition, in order to control for developmental stages, it is suggested that future studies account for the duration of trauma, intensity, types of trauma and the time between the onset of adversity and the time of the assessment of a history of trauma. By identifying the function of stress from those objective

measures, the picture of an adaptive mechanism generating individual differences in sensitivity to stress later in life would become clearer.

3) Experimental methodologies aiming to impose stress on individuals may have differential effects on those with different psychological and psychiatric conditions. The psychological effect which the methods are designed to impose should correspond to the psychiatric or psychological conditions the target sample constitutes. Administration of an experience-specific task condition such as exposure to a script describing personal experiences of childhood trauma may be more effective in generating stress activations, and more informative in relation to underlying hormonal stress reactivity, than the standard experimental procedure of TSST.

How the environmental factor of childhood trauma affects hormonal regulation, and thereby shapes future vulnerability to psychiatric disorders may be explained from a number of facets. Firstly, neuroendocrine sensitivity is critical to predispose in an individual either resilience or vulnerability to future psychiatric conditions. Secondly, perception and appraisal of the level of stress in the face of adverse events may vary stress activations. Objective details of trauma such as duration, intensity and trauma types may help identify how stressful the events are perceived to be. However, how an individual subjectively interprets the event is one of the most important determinants of the function of stress in generating subsequent hormonal activations (Schlotz et al., 2011). Thirdly, the developmental process, including neuroendocrinal maturation and pubertal alterations, may add on or interact with children's ongoing hormonal regulation in response to the experiences of adversity. Fourthly, gender provides critical differences in the hormonal regulation to early life stress and the role of sex hormones influencing the HPA axis regulation during development is one of the intriguing factors to be investigated.

Taking such facets into account, research on hormonal stress reactivity in relation to childhood trauma needs to focus on its process rather than its consequence or cause. In other words, analysing just the outcome value of stress reactivity in a particular sample may not be sufficient to provide an insight into the complex picture of hormonal stress reactivity established through the experiences of childhood trauma. It is noted that a

specific style of hormonal responses manifests as a result of the past accumulation of acute stress responses that generate the adaptation to stressful life events. The mechanism of this adaptation may interact with the multiple factors of predisposition, gender and developmental process. To identify hormonal dysregulation mediating between childhood trauma and depression, the trajectory of this adaptation mechanism should be traced back to bring it to a clear understanding of the effect of childhood trauma. Rather than focusing solely on potential effects on vulnerability to depression, a focus also on the alternative perspective of resilience to depression would make it possible to resolve the conflict between different extant opinions. A long term perspective on hormonal stress reactivity through the life span may thus be a key to solve the puzzle of the effect of childhood trauma on hormonal stress reactivity.

1.4. Introduction: Startle experimental paradigm

The startle reflex is a set of unconscious and automatic bodily movements occurring in response to an aversive stimulation, such as an abrupt sound. It is characterised by the forward thrusting head and its flexor wave reaction descending through the trunk and the knees. This bodily reaction is interpreted as a behavioural expression of the internal state of emotion precipitating a flight-fight reaction to protect organisms from a sudden attack. Startle reflex is also known to reflect the severity of fear in response to the treatments and the conditions imposed in parallel with a stimulus provoking a startle. In preclinical studies, the startle experimental paradigm is therefore used to examine the effects of anxilyotic treatments on rats for their magnitude of bodily startle in the condition where a fear stimulus, such as bright light, is presented with an aversive sound (Walker and Davis, 1997). In humans, eye blink, which is a rapid muscle contraction of the eye lid, is measured as a response variable as this is the fastest and the most stable element in the set of startle reflex. It is recorded by EMG (Electromyogram) and assessed not just for the severity of a single emotional dimension of fear but also for the patterns of the responses modulated by multiple emotional dimensions reflecting a person's ongoing psychological and psychiatric conditions.

The neural pathway that mediates the startle reflex involves four synapses. Three are located in the brain stem including (1) the ventral cochlear nucleus, (2) an area just medial and ventral to the ventral nucleus of the lateral lemniscus, (3) the nucleus reticularis pontis caudalis, and (4) motor neurons in the spinal cord. Auditory input initially enters the nucleus reticularis pontis caudalis via the spiral ganglion cells in the cochlea, and cochlear root neurons. These acoustic neurons send axons through the trapezoid body at the very base of the brain, directly to an area medial and ventral to the lateral lemniscus and continue to the superior colliculus. They then give off axon collaterals that terminate in nucleus reticularis pontis caudalis, which is the level known to be critical for the acoustic startle reflex, onto cells that project to motor neurons which then control the eyblink musculature. (Lopez, 1993).

The amygdala, which represents a central fear system (LeDoux, 1987), then interacts with this neural startle reflex pathway to modulate the startle amplitudes depending on the magnitudes of threat exposure. The amygdala processes fear-related sensory information from all different modalities through its lateral and basolateral nuclei. These nuclei project to the central nucleus of the amygdala, which then project to limbic and brain stem target areas, including the nucleus reticularis pontis caudalis, to mediate fear and anxiety. Since lesions within the central nucleus of the amygdala and the nucleus reticularis pontis caudalis blocks fear potentiated startle reflex (Rosen et al., 1991), this direct pathway is thought to be a main functional system of affective modulation examined, for example, in the startle reflex experimental paradigm.

Since Vrana et al (1988) applied this startle reflex paradigm on human emotion research, it has been extensively utilised in attempts to explain its relationship with psychopathology. Being used along with other objective measures that are interpreted for the inner activation of emotion, such as a neurophysiological measure of ERP (Event-relate-potentials) and physiological measures of heart deceleration and skin conductance, the startle reflex measure is known for the number of experimental advantages that qualify its validity.

Firstly, the mechanism of startle elicitation in relation to the state of fear has been well defined in preclinical studies, which consistently demonstrate that stimuli associating with aversive conditions increase the startle amplitude in rats. From this accumulated preclinical evidence, Davis (1998) described the neural pathway critically involving the central nucleus of the amygdala, which subserves the system of fear startle potentiation. This supposedly most primitive neural circuitry operates the system of the startle reflex, which elicits almost automatically and independently of the control of higher cognitive processing. This system is preserved even in a simple vertebrate, suggesting the startle reflex has been evolved as the most rudimentary defensive reaction and as a trigger to swiftly proceed to protective behaviours against the forthcoming threatening stimuli. For that reason, the startle reflex is assumed to mirror the internal state of fear in anticipation of an aversive event and is regarded as a preparation state for the subsequent action to resolve confrontations. These evolutionary and neurobiological implications validate the use of the startle reflex as a reliable measure for examinations of inner activation of emotion. The inner state of emotion is one of the key cognitive

functions closely associating with psychopathology, which is extremely difficult to objectify and quantify. However, the startle reflex paradigm makes this concept of emotion somehow more tangible and the emotion as a variable more measurable. In addition, startle reflex is relatively free from cognitive distortion such as response biases and demand effect. Verbal reports of subjective feelings are major sources of the behavioural expression of emotion that is frequently used in examinations and diagnoses of individuals in clinical studies. However, these methods may seriously confound a systematic variable of voluntary control and the reports, therefore, may not entirely be reliable to represent an individual's inner state of emotion. The evidence illustrating the neural substrates of startle reflex and its subserving automaticity of the responses could verify that the startle reflex paradigm is resistant to such voluntary control and support the reliability of the paradigm as a standard objective measure.

Secondly, the fact that the robust pattern of affective startle modulation has been consistently demonstrated in previous studies on healthy individuals validates the application of the paradigm to various psychological and psychiatric conditions. This establishment of the healthy norm in affective startle modulation enables us to comparatively interpret the startle responses of psychiatric patients against that norm. In healthy individuals, the startle reflex is potentiated with a concomitant presentation of negative-toned stimuli, while it is attenuated with that of positive-toned stimuli, relative to neutral stimuli. The mechanisms that underlie this linear pattern of affective modulation (positive-neutral-negative) is explained in that the biphasic affective tones induced by the foreground stimuli differentially influence the amplitude of the defensive bodily response of startle reflex (Bradley et al., 2001; Bradley et al., 1993). Negative affect induced by an aversive condition which is congruent to the aversive stimulation of auditory probe operates as a prime and enhances defensive responses. Whereas, positive affect induced by a pleasant condition which is incongruent to the aversive probe counter-regulates and inhibits those responses. Deviation from this systematic affective modulation of the startle reflex is assessed in psychiatric patients and interpreted as a possible behavioural marker of the symptoms of their disorders.

1.5 Aim

Aiming to investigate the effect of childhood trauma on the development, or not, of adult depression, the current study will use a number of experimental measures from different disciplines of psychophysiology, neuroendocrinology and behavioural psychology. The main experimental measures are:

1. a psychophyiological measure of startle responses generated during viewing of images with varying emotional contents is used. Affective modulation of startle responses is examined and how emotional processing styles of affective modulation mediate the relationship between childhood trauma and depression is investigated.
2. a neuroendocrinological measure of cortisol responses to stress caused by viewing various emotional images shown in the startle experiment is used. The level of cortisol increase after the image viewing was measured and how this cortisol response mediates the relationship between childhood trauma and depression is investigated,
3. a behavioural measure of facial emotion recognition in which individual differences in efficiency at identifying facial emotions are examined is used. Efficiency to recognise facial emotions was examined and how it mediates the relationship between childhood trauma and depression is investigated,

The current study focuses on emotional processing of how an individual reacts to and/or recognises emotional stimuli of emotionally laden images and facial expressions. Additionally it will examine a neuroendocrinological component of emotional responses in the form of cortisol reactivity to stress imposed by viewing stressful images.

Those emotional responses will be examined in a cross-sectional study involving groups of depressed and healthy individuals with and without a history of childhood trauma. Specifically, the interactive effect of depression and childhood trauma is the focus of this thesis.

In addition, by using these multiple concurrent experimental measures, the current study aims to examine the relationship between the experiences of childhood trauma and adult onset of depression from the connective view of both psychophysiology and neuroendocrinology. Specifically, it aims to explore the four issues the previous behavioural studies on the effect of childhood trauma had failed to address.

1) The study uses a retrospective design to investigate the relationship between early life experiences of childhood trauma and the adult outcome of a diagnosis of depression, in contrast to other studies that have studied children before the onset of adult illness or used non-clinical samples.

2) Patients with diagnoses of depression and healthy controls with and without experience of childhood trauma will be recruited for the study. Resilience to depression within healthy abused individuals and vulnerability to depression within depressed abused individuals will be considered in this sample strategy.

3) It is ensured that abused samples would cover individuals with diverse trauma types such as physical, sexual and emotional abuse and emotional neglect by examining their responses on the Childhood Trauma Questionnaire, which is a well-validated and standardised battery (Bernstein and Fink, 1998). The studies will examine both the uniform effect of all trauma types together and some separate effects of each trauma type.

4) Both psychophysiological responses of startle reflex and hormonal responses of cortisol to the presented emotional stimuli will be examined in parallel.

To my knowledge, this is the first study that will be able to give answers to these four crucial lines of enquiry in emotion research on childhood maltreatment. It is expected to deliver further evidence illustrating the “brain-behaviour” relationship that has intensely been discussed but not yet sufficiently examined in this field of research.

2.1. Experiment 1: Affective startle modulation

Affective startle modulation in childhood trauma: resilience and vulnerability to depression

Abstract

Background and aims

Previous studies suggest a lack of normal affective modulation in depressed individuals, which reflects their insensitivity to respond flexibly to different emotional contexts. The current study examined emotional processing, using an affective startle modulation paradigm, to clarify its mediatory role in the relationship between early life stress (childhood trauma) and the later development of depression in some individuals as well as a resilience to depression in others.

Methods

The study involved 14 healthy abused and 23 healthy non-abused participants; and 15 abused and 12 non-abused depressed patients. Their startle responses to the auditory probes at 500ms (early) and 3500ms (late) after the onsets of a variety of emotional images (positive, neutral, negative and childhood trauma-related) were measured using electromyography (EMG) of the left orbicularis oculi.

Results

There was a significant startle modulation in healthy individuals at the late probe condition, with a linear pattern from positive through neutral to negative images. However, this startle response pattern of affective modulation in depressed patients was absent. In non-depressed individuals with a history of childhood trauma, there was a significant interaction between the probe condition and emotional valence on the startle amplitudes, with particularly larger response amplitudes to the negative images, giving a pattern of more pronounced affective modulation.

Conclusions

The study adds further evidence of dysfunctional affective startle modulation in depression. Furthermore, we found that abused individuals who were resistant to developing depression showed a particular pattern of a strong normal affective modulation. This is considered to reflect their ability to respond flexibly to emotional variations, hence protecting against the negative bias that may underpin the

development of depressive symptoms. Such a pattern may confer resilience to depression following childhood trauma, and has implications as a potential novel therapeutic target in such patients.

2.1.1. Introduction

The startle reflex paradigm has been used to examine individual differences in the emotional processing of different affect-toned stimuli and their impact on individuals in relation to a number of psychiatric and other medical disorders (Bartley et al., 2009; Seignourel et al., 2007). The startle research on psychiatric disorders ranges from clinical states, including PTSD (Cuthbert et al., 2003; Grillon et al., 1998), anxiety disorder (Kumari et al., 2001; Melzig et al., 2007), psychosis (Giakoumaki et al., 2010; Volz et al., 2003) and depression, to non-clinical (Chan et al., 2007; Mneimne et al., 2008) or premorbid states of personality variability (Larson et al., 2007). Among them, a substantial body of research in both clinical and sub-clinical depression has been recently accumulated (Allen et al., 1999; Dichter and Tomarken, 2008; Dichter et al., 2004; Forbes et al., 2005; Kaviani et al., 2004). The converging evidence from this research offers some important implications for the neuropsychological correlates of depression, suggesting an underlying dysfunction in emotional processing.

Due to the adjustable nature of the paradigm, the startle experimental design has been diversely modified in order to address different research questions set by different researchers. In particular, the time at which the startle probe is administered after presentation of the preceding emotional stimulus has been varied in order to examine specific hypotheses with regard to emotional processing. The timings of the startle probe are critical for the examinations of emotional processing, which recruits different levels of the attentional system. Bradley (2006) explains that, at the level of unconscious processing where the startle probe is presented at between 300ms and 1000ms after stimuli onsets, affective impact rather than affective valence of the foreground stimuli influences the magnitude of startles. In this early attentional window, attentional resources would mostly be allocated to more affectively engaging tones of stimuli such as positive and negative polarity than to a neutral tone. Startles are then inhibited for the former relative to the latter because most of the attentional resource is occupied by their affective impact and little remains to process the startle probe. However, as the timings of the startle probe slide further to 1500 ms and or longer (1500-6000 ms) after the stimuli onsets, startles become increasingly more sensitive to

affective valence than affective impact. In this late attentional window, startles are enhanced for a negative tone but inhibited for a positive tone of the foreground stimuli relative to a neutral tone. As the physiology of the defensive mechanism begins to take effect while the stimuli are more consciously processed with a longer period of presentation, a linear trend of affective modulation starts to emerge (Bradley et al., 2001; Bradley et al., 1993).

Previous studies on depressed patients found this linear trend of affective startle modulation disappears within their overall blunted responses at the level of late processing. This phenomenon is evident when the auditory probe is positioned at 3500 to 7500ms after the onset of an emotional picture stimuli (Allen et al., 1999; Dichter and Tomarken, 2008; Dichter et al., 2004) and during watching film clips (Kaviani et al., 2004). However, this physiological characteristic of depression is not demonstrated at the early processing level as no significant difference is reported in the response patterns between healthy individuals and depressed patients when startles are probed at 300ms after the preceding stimulus (Dichter and Tomarken, 2008; Dichter et al., 2004). In studies of childhood-onset mood disorders, affective modulation was also found to be absent when the number of recurrent depressive episodes is high (Forbes et al., 2005), and comorbidity of depression in other psychiatric disorders is reported (Taylor-Clift et al., 2011). In contrast, studies on healthy individuals with non-clinical depressive symptoms remain rather inconsistent. For example, Cook (1991) suggests from their study of a healthy sample that the depressive state is, in fact, characterised by the tendency to show increased startle amplitudes in response to negative images to form the linear trend of affective modulation. Conversely, the responses of those who score high in neuroticism, which is one of the personality variables that predispose to clinical depression, were not significantly different from the normal linear trend of affective modulation (Chan et al., 2007; Kumari et al., 1996). Other studies on healthy individuals, however, are in line with the clinical startle literature and have found an absence of the linear trend of affective modulation in those with a non-clinical state of depression (Mneimne et al., 2008; Sloan and Sandt, 2010). This discrepancy in results could be due, at least in part, to a heterogeneous nature of sub-clinically depressed populations.

DSM-IV specifies the symptomatology of MDD (major depressive disorder) as excessive negative affect and deficient positive affect (e.g. anhedonia), suggesting observable deficits in emotional processing or emotional reactivity associated with those symptoms. Previously, two groups of authors attempted to conceptualise these emotional features of depression. Clark and Watson (1991) and Rottenberg et al (2005) suggest that depression can be viewed as an overall lack of emotional and autonomic responsiveness. Their claims theoretically fit the previous evidence on depressed individuals whose startle mechanism does not appear to be functionally responsive to produce affective modulation. Previous startle evidence demonstrates that the ability to modulate startle responses to different affective tones, which reflects flexibility in processing and responding to emotional information, is dysfunctional in depressed individuals (Allen et al., 1999; Dichter and Tomarken, 2008; Dichter et al., 2004; Kaviani et al., 2004). Physiological characteristics such as lack of flexibility may be a key functional contribution to the development of the characteristic symptoms and dysfunctional behaviours of depression. The symptom of pervasive anhedonia, including a loss of interest or pleasure, together with a feeling of helplessness may develop from the rigid preconception and misconception of a negative bias (Beck, 1976). Automatic physiological responses to changes in different affective tones should normally play a role in enabling one to acknowledge the emotional contexts of environments positively and negatively at balance. However, the capacity to swiftly shift attention from the negative tone to the positive tone of external stimuli may be compromised in depressed individuals as is suggested from their absence of affective modulation. Consequently, the way the individuals see the world will be diverted in an atypically negative direction; such negative bias may develop further to override an individual's thought patterns, as is observed in depressive states.

The current study employs a startle reflex paradigm to examine emotional processing to clarify its mediatory role in the relationship between early life stress (childhood trauma) and later development of depression. Epidemiological studies show a remarkably high proportion of depressed individuals report having experienced childhood trauma (Chapman et al., 2004). Altered emotional processing, and specifically the negative bias observed in depression, may mediate this causal relationship between childhood trauma and depression. The current study also examines both the effects of attention, using early probes, and affective modulation, using late probes, on individuals' startle

responses. With early probes, i.e. in the early attentional window, startle responses should be suppressed by the emotional impact of the foreground images. With late probes, in the late attentional window, negative foreground images normally enhance whereas positive foreground images inhibit startle responses in the late attentional window, both relative to startles elicited during neutral background images. In addition, by including self-referential images suggestive of childhood trauma as experimental materials, whether specific sensitivities to those images influence the startle magnitudes within abused individuals is also examined. To our knowledge, this is the first study that investigates cognitive resilience and vulnerability to depression as a function of childhood trauma by examining individual differences of affective modulation in startle responses.

Based on previous literature in clinical depression (Allen et al., 1999; Dichter and Tomarken, 2008; Dichter et al., 2004; Kaviani et al., 2004), a lack of affective startle modulation is predicted in depressed individuals with or without a history of childhood trauma. There is no affective literature in abused, non-depressed, healthy individuals. The individuals who remain healthy despite the potentially damaging effect of childhood trauma may possess some cognitive resilience to enable them to respond flexibly to emotional environments, which prevents an atypically negative bias leading to depression. Such greater automatic responsiveness to emotional stimuli, specific to resilient individuals relative to vulnerable individuals, should be reflected in a normal linear affective startle modulation from positive through neutral to negative stimuli.

2.1.2. Methods

2.1.2.1. Participants

Out of the data of 83 participants who were recruited for the one afternoon experimental sessions, the data of 64 participants (22 males and 42 females) were used for the analyses: 14 healthy abused (H/A) and 23 healthy non-abused participants (H/NA); and 15 abused (D/A) and 12 non-abused depressed patients (D/NA). The data of 19 participants were not entered into the analyses because sufficient response amplitudes were not detected in those participants' responses. A statistical power analysis was

performed for sample size estimation based on data from a published study (Heim et al., 2002) examining correlations between childhood trauma and stress reactivity. The effect size in this study was 0.35. With an alpha = .05 and power = .8, the projected sample size (GPower 3.0.8) is approximately N = 64. Thus our proposed sample size of 64 was adequate for the main objective of this study investigating the possible mediatory roles of startle reflex function between childhood trauma and depression by using mediation analyses.

All depressed patients were either currently admitted to or discharged from a hospital with a diagnosis of Depressive Episode or Recurrent Depressive Disorder using the criteria of International Statistical Classification of Diseases and Related Health Problems (ICD-10). In addition, for a depressive episode to be sufficiently severe to be included required a current score above 14 on the Inventory of Depressive Symptomatology (QIDS-SR). All depressed patients were recruited from in- and out-patient facilities of the South London and Maudsley NHS Foundation Trust.
Healthy participants were recruited by advertisement at and around the hospital and university sites. They were required to be free from a personal history of any psychiatric disorder, and to have no psychiatric disorder in first degree relatives.

Additional inclusion criteria for all subjects were: age range between 20 and 65 years old; the absence of neurological disorders; and no history of substance misuse within the previous 2 years. Participants were not required to be completely medication free; antidepressant medication in patients was allowed to be continued for ethical reasons (See Appendix 1 for the list of the use of antidepressants).

The participants were invited to a screening session (general health monitoring) prior to the test, and were administered Childhood Trauma Questionnaire (CTQ : Bernstein et al., 2003) to assess their experiences of childhood trauma. Those who scored at or above 'moderate-severe' level in at least one of the five subscales (emotional abuse (EA), physical abuse (PA), sexual abuse (SA), emotional neglect (EN) and physical neglect (PN)) of the CTQ were then assigned to abused groups (H/A or D/A) and remaining participants were assigned to non-abused groups (H/NA or D/NA).

The study was approved by the National Research Ethics Committee London – London Bridge (Ref no 11/LO/0844). All participants provided written informed consent for their participation in the study. They were compensated for their time and travel.

2.1.2.2. Self-report assessment

All participants completed a battery of self-report assessments measuring the following current psychological and psychiatric conditions after the completion of the laboratory testing session as noted in Table 2.1.1.

Measure	**Variable**
Zung self-rating anxiety scale (Zung, 1971)	Anxiety
Rosenberg Self-esteem Scale (Rosenberg, 1965)	Self-esteem
Social Readjustment Rating Scale (Holmes and Rahe, 1967)	Current stressful events
The Impact of Event Scale – Revised (Weiss and Marmar, 1996)	Post-Traumatic Stress Disorder (PTSD) symptoms
Dissociative Experiences Scale (Carlson et al., 1993)	Dissociative symptoms

Table 2.1.1. Self-report assessments and their measured variables

2.1.2.3. Stimuli development and selection

Ninety-six digital colour images were used as visual stimuli. Seventy-two of these, with positive (24 images), neutral (24 images) or negative valence (24 images), were chosen from the International Affective Picture System (IAPS; Lang, Bradley, Cuthbert, 1995) (See examples in Appendix 2) on the basis of their published affective valence and arousal ratings. The remaining 24 were childhood trauma-related images, selected from an initial pool of 38 images taken from the public photo archive (www. Istockphoto.com) (See an example in Appendix 3).

Selection of 24 childhood trauma-related images, out of 36 initial images, was based on ratings obtained from 8 healthy individuals, who rated the severity and category of abuse that the images were portraying. Severity was rated between 1 (not severe at all) and 10 (extremely severe) score on a likert scale. Twenty-four images (6 images each for the four trauma types of emotional abuse, physical abuse, sexual abuse and emotional neglect) out of 36 images were then selected on the bases of there being a clear categorisation of the individual trauma types (i.e. that it was clear to raters which type of abuse was being represented). Of the clearly categorised images, those with the highest severity ratings were then selected. Mean severity rating scores compared between selected and non-selected images for each trauma type are plotted in Figure 2.1.1.

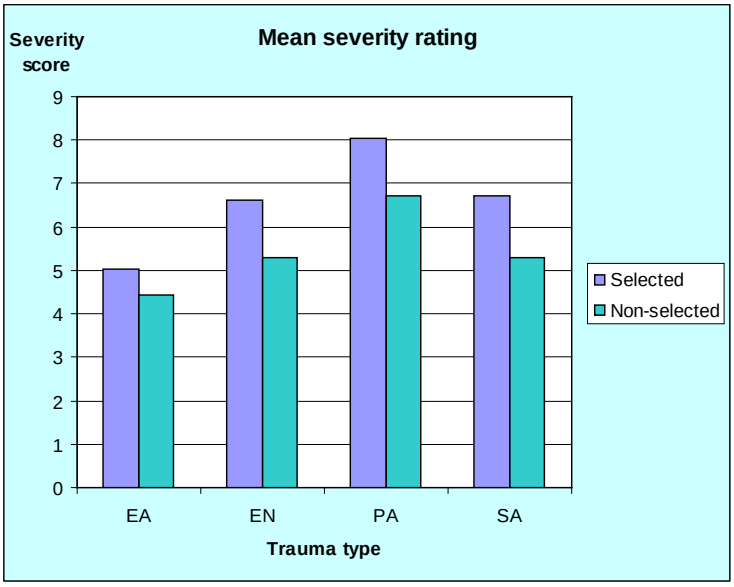


Figure 2.1.1. Mean severe rating scores compared between selected and non-selected images in each trauma type (EA- emotional abuse, EN- emotional neglect, PA-physical abuse and SA- sexual abuse)

2.1.2.4. Stimulus presentation

The presentation of each digital colour image and blank near-black screen (1024 X 768 pixels, JPEG format) was controlled by a Benq slide projector (Model W100) which projected each image approximately 2 metres in front of the participants onto 60 x 90 cm viewing area.

Each participant viewed 96 photographic images interspersed with 24 blank images per session, divided into two balanced image blocks. Each block contained 12 positive, 12 neutral, 12 negative and 12 trauma-related images and 12 blank screens. Within each block the images and blank screens were ordered pseudo-randomly in the PowerPoint software. Eight out of 12 images within each category were accompanied with an acoustic startle probe, presented at 500 ms or 3500ms following the image onset. Ten out of 12 blank images were also accompanied with acoustic probes to increase the unpredictability of startle probes. Within each block, 4 images/per category and 5 blank images were accompanied with early and a similar number with late onset probes. Each photographic and blank image was presented for 6s with an inter-stimulus-interval of 3s-9s; the blank image was also on the screen during the ISIs.

A computerised startle system (SR-HLAB, SDI, San Diego, CA, USA) controlled the acoustic probe presentation. The acoustic startle stimuli consisted of 50-ms bursts of 95-dB white noise with near instantaneous rise time, delivered binaurally over closed-cup, calibrated Telephonics (TDH-39-P, Maico) headphones. A 70dB white nose background was constantly present throughout the image viewing.
Electromyographic (EMG) activity of the left orbicularis oculi muscle was recorded via two surface 6mm disc electrodes (Ag/AgCI) filled with Dracard electrolyte paste (SLE, Croydon, UK).

Raw EMG signals were recorded, amplified, filtered, rectified and stored by the same computerised startle system controlling acoustic startle presentation (SR-HLAB, SDI, San Diago, CA, USA) and image display. The sampling rate was set at 1000hz (sample internal (ms) =1; number of samples per trial = 121) over 250ms following startle probe onset. The lower band pass filter (1-500Hz) provided by the equipment was selected. For each individual trial (probed screen), a baseline was calculated by the program taking the average of the minimum and maximum value recorded during the first 20ms (the first 20 data points) following startle probe onset. Using same method, the program calculated the average amplitude across the entire response window (0-120ms). These two values were used then by the program to identify valid peaks, and to calculate response (EMG) amplitude (in arbitrary analogue-to-digital (A/D) units) and response peak latency (in ms). Response amplitude was the maximum point of valid response peaks occurring 20-120ms after startle probe onset (0ms). For each individual probed

screen trial, valid response peaks were scored if their amplitude was at least twice great as the standard deviation of the entire response window plus the baseline. Latency to response peak represents the time interval (ms) between startle probe onset and maximum point of a valid response peak. Individual trials were excluded from analysis if no valid response peak was detected, or if excessive background interference was evident in the manual process to score each trial response.

2.1.2.5. Procedure

Participants were told that the aim was to assess their eye blinks while they viewed a series of images. They were told that they would hear occasional noise bursts while they were viewing the images but were instructed to ignore them. The electrodes and headphones were then attached and participants were asked to keep a comfortable position in an armchair and to stay still throughout the viewing session. Two electrodes were applied below the left lower eyelid and one electrode was placed over the left mastoid behind the left ear.

2.1.2.6. Subjective ratings

Upon the completion of startle session, participants' self-ratings of pleasantness, arousal, interest and stress level for each image used in the startle experiment, were obtained using a computerised task. The presentation of the images and questions asking for the ratings on those images were written in SuperLab (visual stimuli presentation software) on the 15 inch screen of a Toshiba Satellite Pro P300-1CV 15-inch laptop computer. Each image was presented prior to the questions, until the participant pressed a key on the keyboard to continue to the question; i.e. they were allowed to view the picture as long as they liked. Then the screens of four questions, each with a likert scale, appeared one by one. The participants were asked to press the number key on the keyboard in indicating their answers to the questions. The four questions appeared successively each time they pressed the key to provide their answer. When the forth question was answered by pressing the key, the next image appeared. The order of the questions with the likert scale was:

1.‘ How pleasant did you find the picture’ (-4 extremely unpleasant – 4 extremely pleasant),
2.“How excited did you feel when you saw the picture” (1 extremely calm – 9 extremely excited),
3.“How interesting did you find the picture” (1 not interesting at all – 9 extremely interesting) and
4.“How stressful did feel when you saw the picture?” (1 not stressed at all – 9 extremely stressed).
The order of the presentation of each image with its questions was the same as in the startle experimental session. Participants’ responses (answer and reaction time) were recorded by SuperLab and subsequently analysed.

2.1.2.7. Statistical analysis

All above statistical analyses were carried out using SPSS v20. The level of significance was set at p=0.05 unless stated otherwise.

To examine possible mediatory roles of the startle reflex between childhood trauma and depression, mediation analyses were conducted within the predictor variable of childhood trauma (CT: A/NA), current depressive state measured by QIDS-RS (Dep) and startle amplitudes with different conditions of Probes (500ms/3500ms) by Valence (positive, neutral, negative and childhood trauma-related (CT)).

In addition, to examine possible group differences in startle variables, a three-way mixed 2 (Probe: 500ms, 3500ms) x 4 (Group:H/A, H/NA, D/A and D/NA) x 4 (Valence: positive, neutral, negative, childhood trauma-related) ANOVA was conducted on the dependent measures of the startle response amplitudes and latencies. Significant main and interactive effects were examined with further lower order ANOVAs and the analyses of simple main effects.

For each rating score (pleasantness, arousal, interest and stress) and imaging viewing time in the subjective rating task, a two-way mixed ANOVA (Group x Valence) was

conducted. Significant interactions and main effects were followed up by appropriate planned contrasts and post-hoc Bonferroni analyses.

Prior to running the analyses described below, relevant variables were examined to check that the assumptions required for the above analyses were met in this data set.

2.1.3. Results

2.1.3.1. Demographic data

Demographic data for the total of 64 participants is presented in Table 2.1.2. As is shown, the four groups did not differ with respect to age, gender and recent stressful events. As expected, the abused groups (H/A and D/A) had higher mean scores for all trauma (CTQ) subtype scales than the non-abused groups. Similarly, the patient groups (both with and without abuse) had higher current anxiety, PTSD, depressive and dissociative symptoms, and lower self-esteem than the healthy groups.

Table 2 Participant Characteristics

	H/A (n=14)	**H/NA (n=23)**	**D/A (n=15)**	**D/NA (n=12)**	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Statistics
Age (year)	43.0 (12.9)	45.0 (13.9)	50.46 (12.1)	50.8 (11.4)	NS
Gender	M:6, F:8	M:8, F:15	M:4, F11	M:4, F:8	NS
CTQ					
EA	12.0 (3.9)	5.9 (1.4)	15.0 (5.5)	6.8 (2.1)	$F(3, 60) = 25.2, p < .001$
PA	10.9 (5.3)	5.3 (.5)	8.1 (4.4)	5.3 (.8)	$F(3, 60) = 9.8, p < .001$
SA	8.0 (4.0)	5.0 (.2)	8.2 (5.2)	5.0 (.2)	$F(3, 60) = 5.1, p < .01$
EN	13.4 (4.1)	6.7 (1.7)	17.9 (4.3)	9.2 (3.2)	$F(3, 60) = 37.4, p < .001$
PN	7.7 (2.9)	5.7 (1.3)	8.8 (3.6)	5.6 (1.1)	$F(3, 60) = 6.4, p < .01$
CTNO	2.2 (1.3)	0	2.4 (1.2)	0	$F(3, 60) = 36.9, p < .001$
ZAS	29.2 (4.8)	27.6 (4.1)	40.8 (8.5)	43.6 (12.8)	$F(3, 60) = 17.3, p < .001$
RSS	22.8 (4.6)	22.8 (4.3)	9.6 (3.7)	10.5 (6.9)	$F(3, 60) = 36.5, p < .001$
SRRS	1.7 (.9)	1.5 (.7)	1.3 (.8)	1.9 (1.2)	NS
IES-R	19.5 (16.1)	12.7 (11.4)	37.0 (14.9)	40.4 (18.5)	$F(3, 60) = 13.3, p < .001$
QIDS-SR	12.1 (6.2)	5.6 (3.1)	40.6 (13.9)	34.9 (17.2)	$F(3, 60) = 43.4, p < .001$
DES	6.8 (6.3)	4.2 (3.4)	13.4 (14.1)	18.7 (18.7)	$F(3, 60) = 5.3, p < .01$

Statistics are one-way ANOVAs with a between-factor of the groups (Con/A, Con/NA, Dep/A and Dep/NA) on the variables of age, gender, CTQ subtypes, the number of CT (CTNO) and the self-report assessment scores. (EA – Emotional abuse, PA – Physical abuse, SA – Sexual abuse, EN – Emotional neglect, PN – Physical neglect, ZAS – Zung Anxiety Scale, RSS – Rosenberg Self-esteem Scale, SRRS – Social Readjustment Rating Scale, IES-R – The impact of Event Scale Revised, QIDS-SR – Inventory of Depressive Symptomatology, DES – Dissociative Experiences Scale) and chi-square test on gender. NS = non-significant

2.1.3.2. Startle measures

2.1.3.2.1. Startle response amplitudes

The series of mediation analyses revealed indirect effects of CT on Dep through different conditions of startle amplitudes.

There was a significant indirect effect of CT on Dep through 500ms x neutral startle amplitudes (b = 1.59, BCa CI (.11, 4.33). This represents a relatively small effect, K^2 = .04, 95% BCa CI (.004, .11).

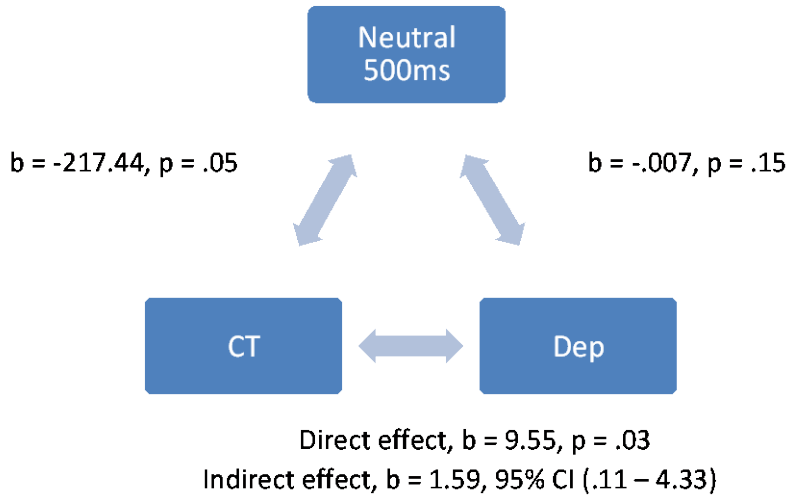


Figure 2.1.2. Model of childhood trauma as a predictor of depression, mediated by 500ms x neutral startle amplitudes. The confidence interval for the indirect effect is a BCa bootstrapped CI based on 1000 samples.

There was a significant indirect effect of CT on Dep through 500ms x negative startle amplitude (b = 1.44, BCa CI (.06, 4.89). This represents a relatively small effect, K^2 == .04, 95% BCa CI (.003, .11).

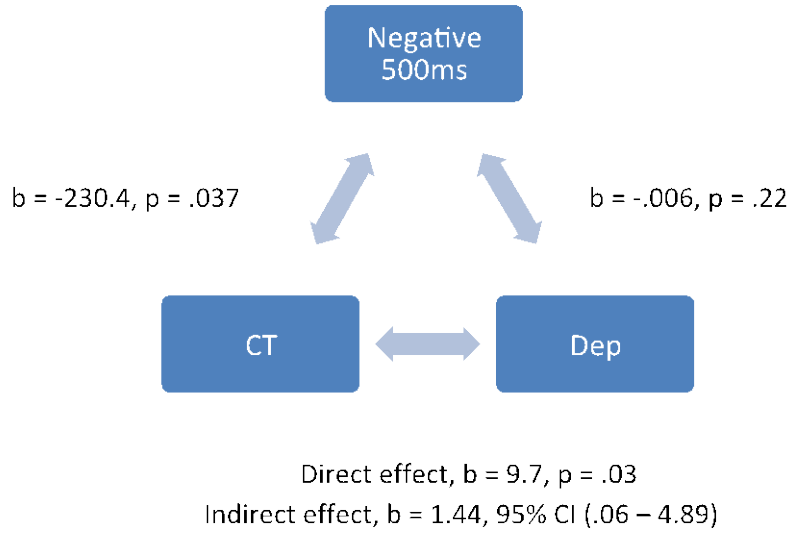


Figure 2.1.3. Model of childhood trauma as a predictor of depression, mediated by 500ms x negative startle amplitudes. The confidence interval for the indirect effect is a BCa bootstrapped CI based on 1000 samples.

There was a significant indirect effect of CT on Dep through 3500ms x positive startle amplitude (b = 1.69, BCa CI (.04, 4.27). This represents a relatively small effect, K^2 == .04, 95% BCa CI (.003, .11).

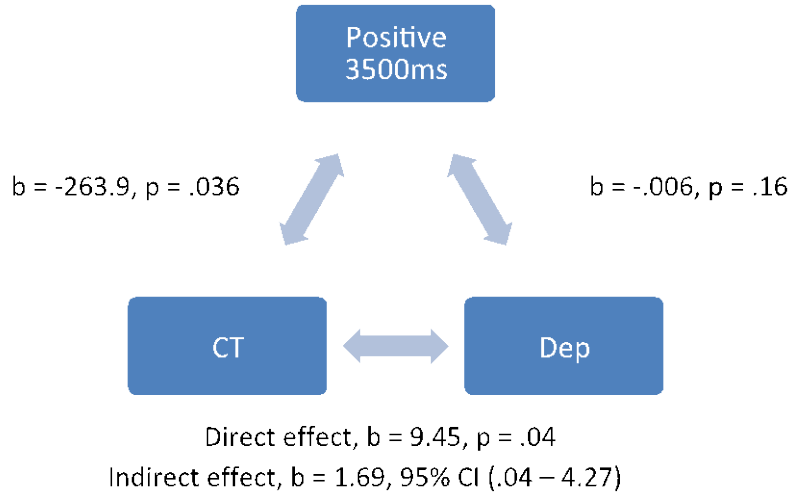


Figure 2.1.4. Model of childhood trauma as a predictor of depression, mediated by 3500ms x positive startle amplitudes. The confidence interval for the indirect effect is a BCa bootstrapped CI based on 1000 samples.

There was a significant indirect effect of CT on Dep through 3500ms x neutral startle amplitude (b = 1.78, BCa CI (.22, 5.08). This represents a relatively small effect, K^2 == .04, 95% BCa CI (.007, .12).

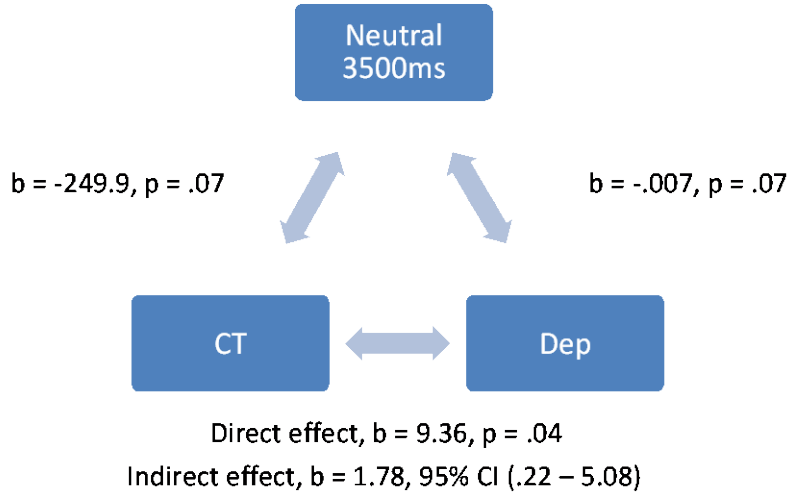


Figure 2.1.5. Model of childhood trauma as a predictor of depression, mediated by 3500ms x neutral startle amplitudes. The confidence interval for the indirect effect is a BCa bootstrapped CI based on 1000 samples.

There was a significant indirect effect of CT on Dep through 500ms x negative startle amplitude (b = 1.54, BCa CI (.07, 4.59). This represents a relatively small effect, K^2 == .04, 95% BCa CI (.002, .12).

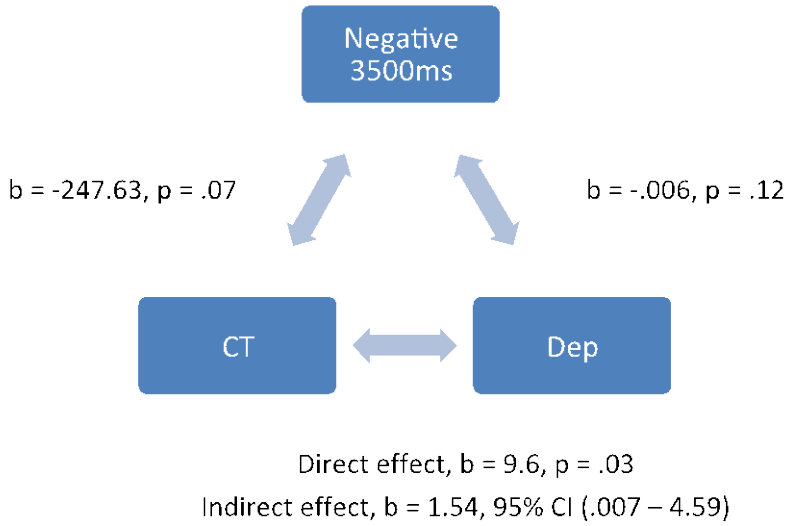


Figure 2.1.6. Model of childhood trauma as a predictor of depression, mediated by 3500ms x negative startle amplitudes. The confidence interval for the indirect effect is a BCa bootstrapped CI based on 1000 samples.

There was a significant indirect effect of CT on Dep through 3500ms x CT startle amplitude (b = 1.32, BCa CI (.004, 4.62). This represents a relatively small effect, K^2 == .04, 95% BCa CI (.003, .12).

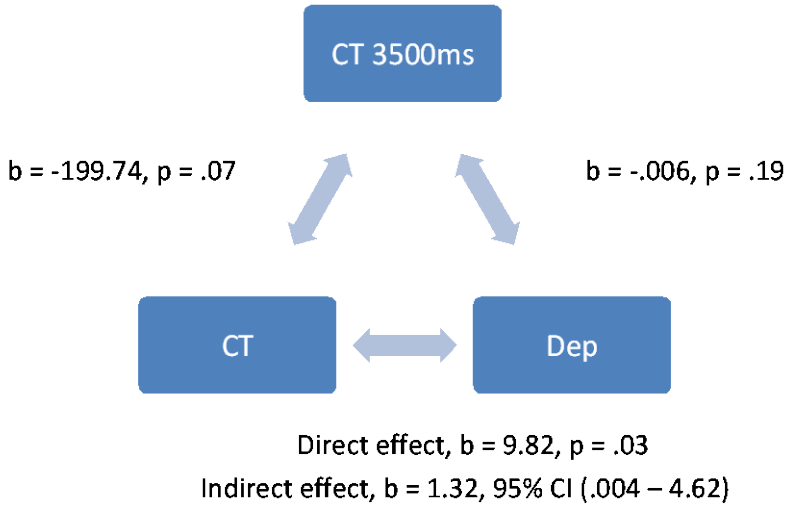


Figure 2.1.7. Model of childhood trauma as a predictor of depression, mediated by 3500ms x CT startle amplitudes. The confidence interval for the indirect effect is a BCa bootstrapped CI based on 1000 samples.

There were no significant effects of CT on Dep through 500ms x positive and 500ms x CT startle amplitude.

A three-way ANOVA (Probe x Group x Valence) on the startle response amplitudes revealed main effects of Probe ($F(1, 60) = 32.04$, $p < .01$), Group ($F(3, 60) = 2.85$, $p < .05$) and Valence ($F(3, 180) = 6.91$, $p < .01$). The main effect of Probe indicated that response amplitudes were larger in the late probe condition of 3500ms than the early probe condition of 500ms across all groups (Figures 2.1.2.a and b). The main effect of Valance showed that the amplitudes were significant larger during neutral ($p < .05$) and negative images ($p < .1$) than positive images, and they were significantly larger for negative than for childhood trauma-related ($p < .05$) across all groups. There was no significant three-way interaction but Group interacted significantly with Valence ($F(9, 180) = 2.4$, $p < .05$) and Probe ($F(3, 60) = 3.07$, $p < .05$)

Separate two-ways ANOVA (Probe x Valence) for each group were conducted specifically to examine the effect of probe onset, yielding a significant interaction ($F(3, 39) = 3.0$, $p < .05$) and main effects of Probe ($F(1, 13) = 10.7$, $p < .01$) and Valence ($F(3, 39) = 5.54$, $p < .05$) on the amplitudes in H/A. These effects suggest that the amplitudes were generally larger for the late probe condition than the early probe condition. Post-hoc Bonferroni pair-wise comparisons on Valence in this group revealed that the amplitudes for negative were significantly larger than for positive ($p < .05$) irrespective of Probe. There were no differences between other pairs. In addition to Probe x Valence analyses, planned T-test contrasts on Probe were conducted separately for each Valence. These revealed the amplitude differences between the probe conditions were more significant in negative ($t(13) = -4.43$, $p < .01$) than in positive ($t(13) = -2.1$, $p < .05$), neutral ($t(13) = -2.3$, $p < .05$) and childhood trauma related (NS), suggesting strong negative potentiation at the late probe condition in this group. No significant interactions were found in other groups.

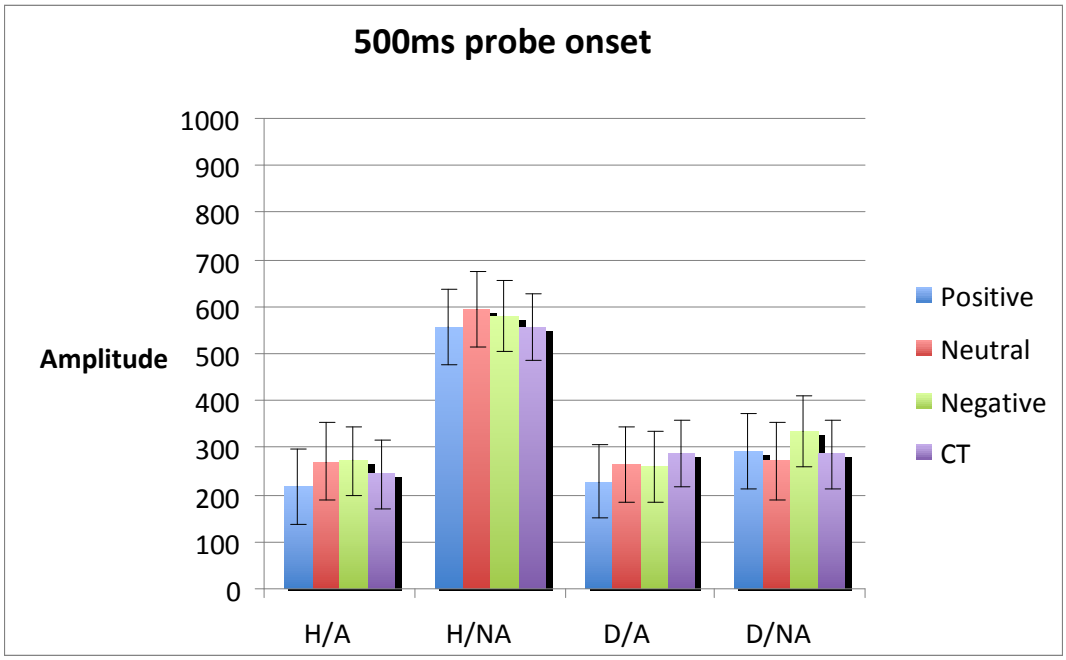
In H/NA, only main effects of Probe ($F(1, 22) = 20.97$, $p < .01$) and Valence ($F(3, 66) = 7.45$, $p < .01$) were found. The amplitudes were significantly larger in the late probe condition than early probe condition. Post-hoc Bonferroni pair-wise comparisons on Valence revealed that the amplitudes were significantly larger for negative ($p < .01$) or neutral ($p < .1$) than for positive, and were significantly larger for negative than for childhood trauma-related ($p = .05$). There were no differences between other pairs.

In D/A, a main effect of Probe ($F(1, 14) = 5.97$, $p < .05$) was found suggesting that startle response amplitude in this group was significantly larger in the late probe condition than the early probe condition across all image categories but there was no effect of Valence at either probe condition.

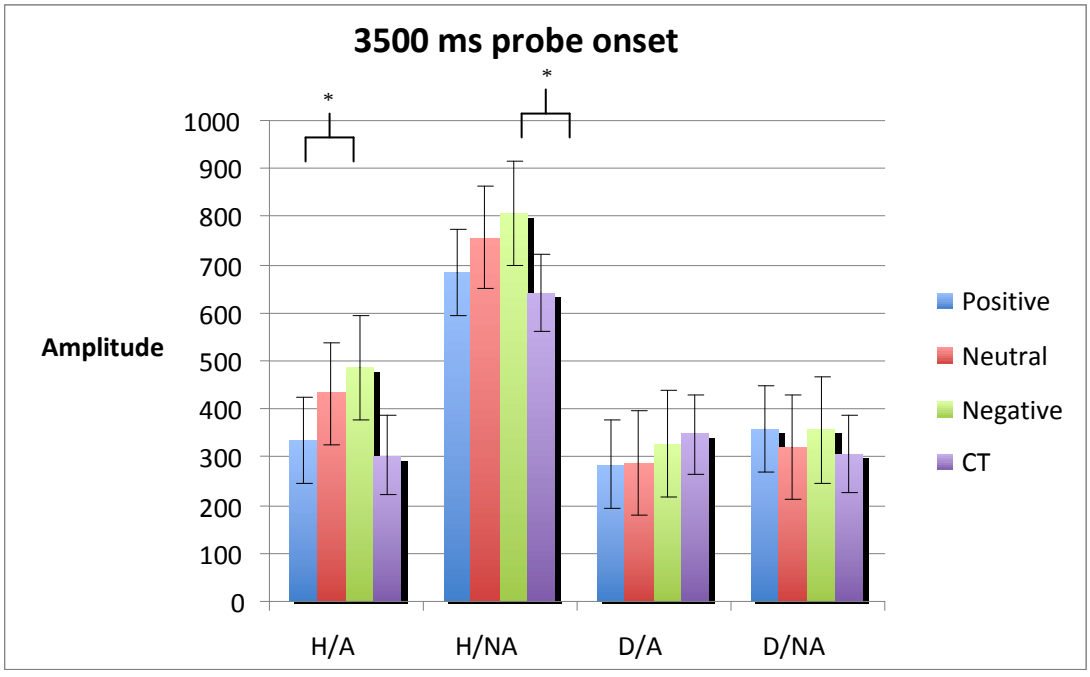
In D/NA, neither main effects (Probe and Valence) nor interaction (Probe x Valence) was found.

Separate analyses of a two-way ANOVA (Group x Valence) for each probe condition conducted to examine the effect of affective modulation yielded no main effect of Group or Valence and no Group x Valence interaction on the amplitudes for the early probe condition (means and standard errors separately for both probe conditions illustrated in Figure 1a and b). However, for amplitudes on the late probes, there were both significant main effects of Group ($F(3, 60) = 3.01$, $p < .05$) and Valence ($F(3, 180) = 6.73$, $p < .01$) as well as a significant interaction ($F(9, 180) = 2.35$, $p < .05$). This interaction remained significant even after the scores of all self-assessment scores (anxiety, self-esteem, current stress, PTSD, depressive symptoms, dissociative symptoms) were entered as covariates ($F(9, 162) = 2.32$, $p < .05$). Planned contrasts of one-way ANOVA on Valence were conducted separately for each Group for this late probe condition. They revealed significant effects of Valence only in the control groups (H/A: $F(3, 39) = 5.27$, $p < .01$, H/NA; $F(3, 66) = 6.07$, $p < .01$); as shown in Figure, a modulation pattern of increasing amplitudes from positive to negative through neutral is present in the control groups but not in the depressed groups. Differences in Valence were particularly significant between positive and negative ($p < .05$) in H/A and negative and childhood trauma-related ($p < .05$) in H/NA as revealed in post-hoc Bonferroni analyses.

Figure 2.1.8.



a) Means and standard errors of startle response amplitudes for the 500ms probe condition for positive, neutral, negative and childhood trauma-related images in the four groups.



b). Means and standard errors of startle response amplitudes for the 3500ms probe condition for positive, neutral, negative and childhood trauma-related images in the four groups. * $p < .05$

2.1.3.2.2. Latencies to response onset

Means and standard deviations for latencies to response onset are presented in Table 2.1.3.

A three-way ANOVA (Probe x Group x Valence) on latencies yielded no interactions but only main effect of Probe ($F(1, 60) = 15.76$, $p < .01$) suggesting all groups were generally slower to respond to the late probe condition than to the early probe condition. There were no main effects of Group and Valence on latencies.

Table 3. Means and standard deviations for latencies to response onset in the four groups

	Positive mean (SD)	Neutral mean (SD)	Negative mean (SD)	CT* mean (SD)
Latencies (ms)				
500ms picutre onset				
H/A	53.25 (16.81)	55.01 (9.82)	52.84 (19.73)	54.18 (20.07)
H/NA	54.75 (11.14)	58.56 (10.80)	58.17 (11.81)	55.54 (11.13)
D/A	47.21 (12.00)	48.05 (14.67)	43.75 (12.70)	46.51 (11.92)
D/NA	60.23 (18.51)	53.49 (11.12)	55.54 (17.12)	48.71 (14.61)
3500ms picture onset				
H/A	52.22 (16.27)	58.50 (20.01)	65.29 (22.15)	59.03 (10.44)
H/NA	60.38 (8.93)	63.38 (9.85)	61.03 (8.44)	60.00 (11.83)
D/A	47.94 (11.37)	48.41 (9.76)	49.03 (9.98)	56.49 (12.60)
D/NA	61.06 (10.97)	61.73 (10.04)	54.07 (14.07)	58.84 (12.97)

2.1.3.3. Subjective ratings

2.1.3.3.1. Imaging viewing time

There was a significant main effect of Valence on the image viewing time ($F(3, 180) = 19.1$, $p < .01$), suggesting the order of viewing time (from longest to shortest) was: childhood trauma related, negative, neutral, and positive images, respectively, across the groups (Figure 2.1.3). There was neither a main effect nor any interaction involving the Group.

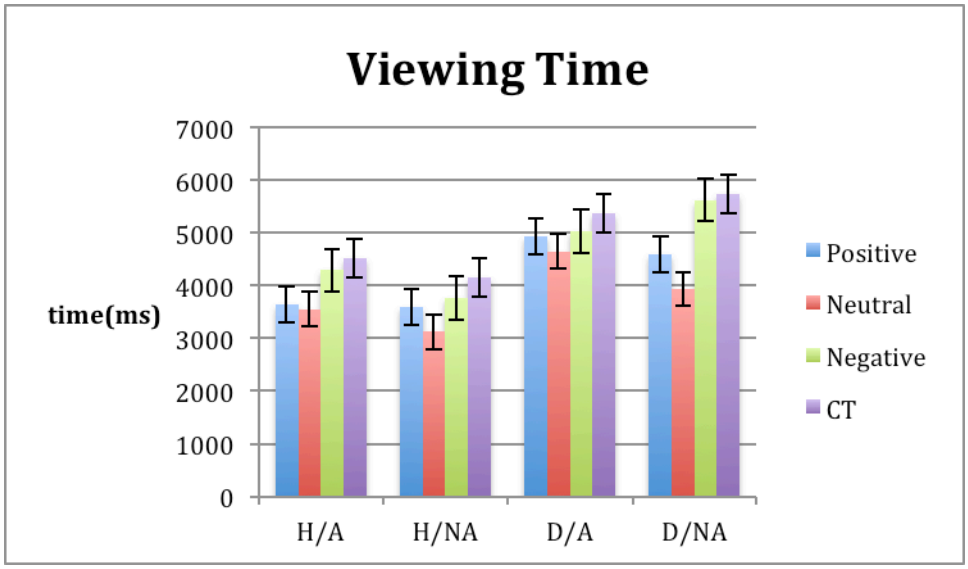


Figure 2.1.9. Means and standard errors of viewing time (ms) in the subjective rating task for positive, neutral, negative and childhood trauma-related images in the four groups

2.1.3.3.2. Pleasantness

For pleasantness ratings, there was a significant main effect of Valence ($F(3, 180) = 398.89$, $p < .01$), suggesting positive, neutral, childhood trauma-related and negative images, respectively, were rated the most pleasant to the most unpleasant, across the groups (Figure 2.1.4). There was neither a main effect nor any interaction relating to Group.

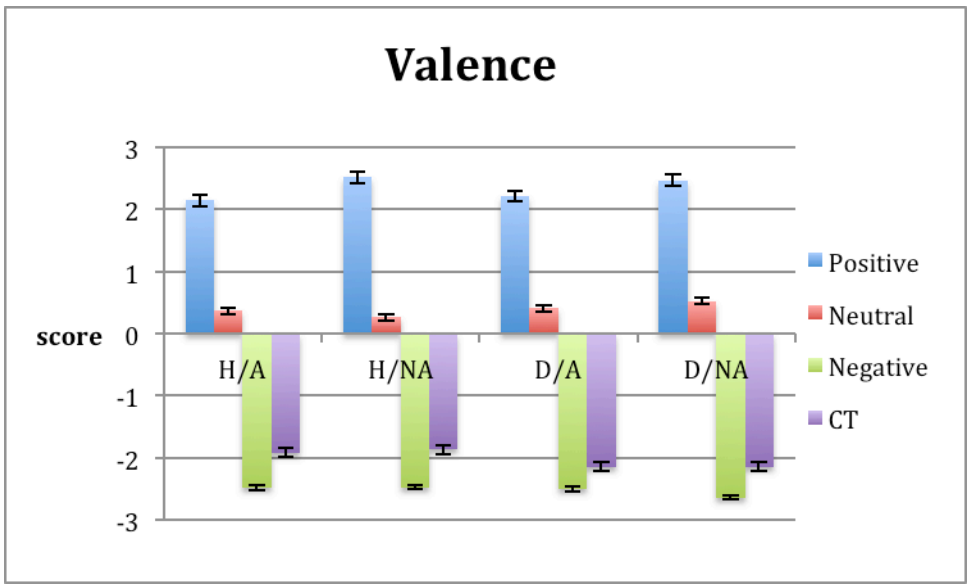


Figure 2.1.10. Means and standard errors of subjective rating scores of pleasantness for positive, neutral negative and childhood trauma-related images in the four groups.

2.1.3.3.3. Arousal

For arousal ratings, there was no main effect of Group but a significant main effect of Valence ($F (3, 180) = 37.33$, $p < .01$) and a significant interaction between Valence and Group ($F (9, 180) = 5.28$, $p < .01$). As shown in Figure 2.1.5, depressed groups rated the negative and childhood trauma-related images more arousing than control groups, but rated positive and neutral images as less arousing than control groups. This trend of interaction was further confirmed by separate analyses on differences between the control groups and the depressed groups for each image. They yielded significant group differences in negative ($F (1, 62) = 6.94$, $p < .05$) and childhood trauma-related images ($F (1, 62) = 7.94$, $p < .01$) but not in positive and neutral image.

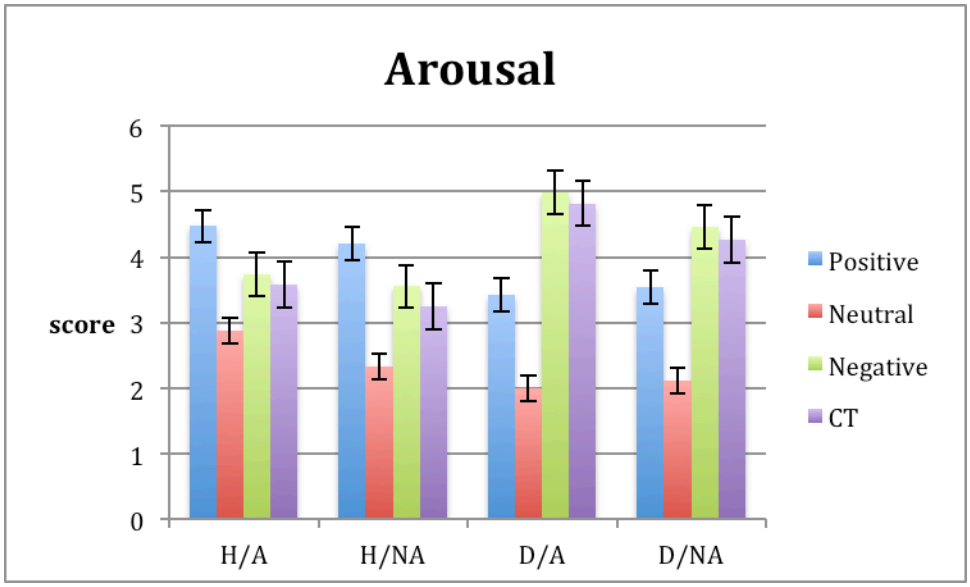


Figure 2.1.11. Means and standard errors of subjective rating scores of arousal for positive, neutral negative and childhood trauma-related images in the four groups.

2.1.3.3.4. Interest

For interest ratings, there was a significant main effect of Valence ($F (3, 180) = 36.92$, $p < .01$), suggesting positive, childhood trauma-related, negative and neutral images,

respectively, were rated the most to the least interesting, across the groups (Figure 2.1.6). There was neither main effect nor interaction relating to Group.

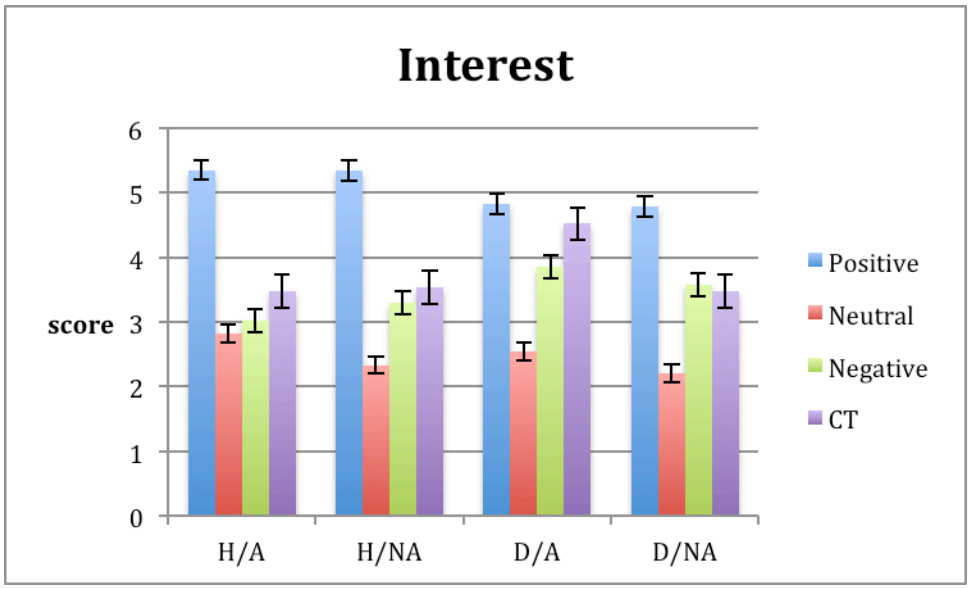


Figure 2.1.12. Means and standard errors of subjective rating scores of interest for positive, neutral negative and childhood trauma-related images in the four groups.

2.1.3.3.5. Stress

For stress ratings, there was a significant main effect of Valence ($F(3, 180) = 256.50$, $p < .01$), suggesting negative and childhood trauma-related images were rated more stressful than positive and neutral images across the groups (Figure 7). There was neither main effect nor interaction involving the Group factor.

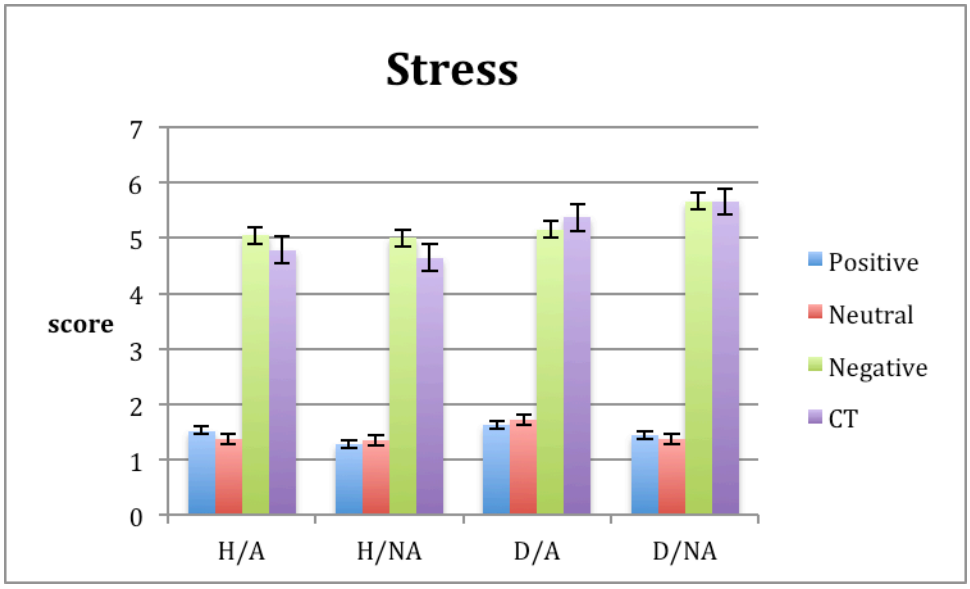


Figure 2.1.13. Means and standard errors of subjective rating scores of stress for positive, neutral negative and childhood trauma-related images in the four groups.

2.1.4. Discussion

The current study examined the effect of attention and affect, using early and late startle probes, on startle modulation in groups of healthy and depressed individuals with and without a history of childhood trauma. At the late probe condition of 3500ms after the foreground picture onset, as hypothesised, a lack of affective modulation was observed in depressed individuals regardless of their history of childhood trauma. In contrast, healthy individuals demonstrated a normal linear pattern of affective modulation regardless of the same history. Mediation analyses on the indirect effect of childhood trauma on current depression state confirmed this lack of affective modulation in depression. Suppressed startle responses, indicating a lack of affective modulation, in response to the images with all valences, at the late probe condition were found to mediate the relationship between childhood trauma and depression. These mediation analyses have shown that startle response amplitudes in response to the images with a variety of valences at the late probe condition and with neutral and negative valence at the early probe condition were decreased in the individuals with a history of childhood trauma. Startle response amplitudes were then negatively correlated with current depressive state, suggesting these suppressed startle functions as a consequence of childhood trauma are playing a role to exacerbate an individual's depressive state. The

mediation analyses revealed that these functional changes in startle responses mediate the relationship between childhood trauma and depression and suggest suppressed startle functions represent a vulnerability factor for depression, whereas the opposite pattern represents resilience to depression. In fact, an interaction between the probe condition and the emotional valence of the images was found only in healthy abused individuals; they showed a significant difference between their patterns of affective modulation at the early versus late probe conditions, reflecting strong negative potentiation at the late probe condition. Thus, the normal pattern of affective modulation – negative potentiation at the late probe condition – is particularly prominent in healthy individuals who have a history of childhood trauma. This greater responsiveness to emotional stimuli implicated in the normal affective modulation is suggested as representing the cognitive resilience of abused but still healthy individuals that enables them to remain healthy despite the potential long term psychological and neurobiological effects resulting from childhood trauma.

2.1.4.1. Absence of startle affective modulation in depression

At the late probe condition, healthy individuals exhibited the well-established linear increase of startle amplitudes across positive, neutral and negative images. In contrast, depressed individuals failed to show this typical response pattern of affective modulation. This is in line with the previous findings that have shown depressed individuals' blunted startle responses across emotional contexts (Dichter and Tomarken, 2008; Dichter et al., 2004; Kaviani et al., 2004; Mneimne et al., 2008). Depressed individuals typically show the characteristics of a negative bias with an inability to attend flexibly to both positive and negative emotional stimuli. The blunted automatic modulation of startle responses reflects inflexibility in those individuals' emotional processing styles. Insensitivity to emotional contexts or a lack of emotional regulation thus contributes to a considerable degree to the development of symptomatic behaviours in which the individuals generate their maladaptive thoughts in an atypically negative direction (Rottenberg et al., 2005).

Another important finding is that the severity of depressive symptoms at the time of participation in the experimental sessions was controlled as a covariate and was shown

to have no effect on the results of this study. Blunted startle modulation identified in the current depressed sample groups may thus be a trait vulnerability, but not a state vulnerability which can be ameliorated as their symptoms progress. The present sample included both admitted and discharged depressed patients. This mixture of depressed patients with different symptom severity may have demonstrated their enduring cognitive dysfunction that sustains even long after their discharge and that contributes to their future recurrence of depressive symptoms. Indeed, previous studies have demonstrated that blunted startle modulation continues to be observed even after successful pharmacological treatments with antidepressants on depressed patients (Dichter et al., 2004). Blunted startle modulation may thus be a marker of vulnerability to depression that persists into later life stages and perhaps serves as a risk factor for its chronicity.

2.1.4.2. Strong normal affective modulation as cognitive resilience to depression

Aside from such replication of previous findings on depression, an important finding in the current study is that the effect of normal affective modulation was prominent in the startle responses of the healthy individuals with a history of childhood trauma. Interestingly, the effect of attention was consistent across the four groups at the early probe condition; i.e. no differences between the groups or emotional valences were observed in this early attentional window. After the most attentional resources were allocated to the foreground images, following startle responses to auditory probes were successfully suppressed equally in both healthy and depressed individuals with a history of childhood trauma at the early probe condition. Typical unconscious processing thus is preserved in both these groups. However, as mentioned earlier, typical affective modulation was shown only in the healthy individuals with a history of childhood trauma but not in the depressed individuals with the same history. These results implicate normal or superior affective modulation as psychophysiological characteristics specific to this particular sample of healthy abused individuals and as cognitive resilience to depression acquired through repeated exposure to the early life stress of childhood trauma.

2.1.4.3. Discrepancy between subjective ratings of and objective startle responses to emotional images

Consistent with previous findings (Dichter et al., 2004; Kaviani et al., 2004), subjective ratings on the images did not correspond to the pattern of group differences demonstrated in the objective measure of startle responses. In fact, all the participants rated the images in a very similar manner. Pleasantness, interest and stress were rated almost identically across the groups. This may be due to the demand characteristics of situations in which they feel they are expected to follow the prototypical manner of responses.

Among the rating categories, arousal was, however, rather interesting as the depressed groups perceived themselves to be significantly more aroused when viewing negative and childhood trauma-related images than the control groups. Conversely, they perceived themselves to be less aroused when viewing neutral and positive images than the control groups, although this group difference did not reach formal significance. A possible explanation for this is that, for the arousal question, the participants' answers more accurately reflect their inner states of feelings because they could describe their autonomic responses of arousal with a more instinctive manner than other rating categories. Increased autonomic sensitivity to negative images in the depressed individuals, however, does not correspond to their diminished startle responses to the same images. Self-rated autonomic responses of arousal and psychophysiological responses of startle may thus be independent and derive from separate functions.

In the current study, images related to childhood trauma were included especially to examine their effect on the individuals with a history of childhood trauma; the expectation was that prominent behavioural characteristics of either increased sensitivity to or avoidance of those images would be reflected in the experimental results. However, group differences were observed in the responses to childhood trauma-related images neither in the startle nor in the self-rating measures. Childhood trauma-related images overall provoked much smaller startle responses than the negative images and did not seem to sensitise the abused individuals' protective mechanism from their recalls of traumatic events. This may be because those images were remotely associated with their own personal experiences, or alternatively because

they provoked a sense of disgust that inhibits startle but not one of threat that enhances startle (Stanley and Knight, 2004). In subjective responses, those images were rated equally unpleasant and stressful to negative images across the groups.

2.1.4.4. Limitations

Anxiety, which is known to provoke hyperstartling (Grillon et al., 1998; Kumari et al., 2001), was not found to have an effect on the current results. Anxiety, which is often comorbid with depression (Angold et al., 1999; Costello et al., 2003), was controlled in the analyses as a covariate, but it did not show an independent effect on startle amplitudes. In clinical startle literature, anxiety is explicitly differentiated from depression with respect to its pattern of startle magnitudes (Kaviani et al., 2004), and its clinical feature of hypersensitivity to emotional contexts has been explained by its startle characteristics of hyper-reactivity (Grillon, 2002). It is therefore rather perplexing that anxiety did not seem to affect startle responses in present results. A possible explanation for this is that sedative effects of antidepressants may have overridden anxiety effects in the current depressed sample groups. Medication was monitored but was not strictly controlled as almost none of depressed patients were unmedicated in the current study. Anxiety may thus not be explicitly present in the current depressive sample groups to show a sufficient effect to increase startle amplitudes to emotional stimulations.

Another limitation in the present findings is that the current study design with a retrospective report of childhood trauma does not allow to clarify whether the cognitive resilience identified is environmentally acquired or genetically predisposed. Startle mechanism is regulated, though not exclusively so, by the amygdala, which is one of the rudimentary brain areas whose function has already been almost fully developed at birth (Shaw et al., 2008). Thus, in theory, the function of affective modulation may not be largely modified by environmental factors during development and the possibility of acquired resilience is ruled out in this case. However, the prefrontal cortex, which matures relatively slowly throughout adolescences into early adulthood (Yurgelun-Todd, 2007), is also known to make considerable functional contributions to emotional regulation. Its role in emotional regulation is supported by evidence of cortical

activation occurring concomitant with affective startle modulation (Bianchin and Angrilli, 2012) and of cortical control over emotional processing through increased integrity of functional connections between cortical and subcortical structures (Herba and Phillips, 2004). These prefrontal involvements in the development of affective modulation, thus suggest the possibility of acquired resilience linked to the environmental effect of childhood trauma mediated most likely via the prefrontal cortex. Further clarification of neural correlates of affective modulation or a prospective study design to trace forward the development of affective modulation may elucidate how cognitive resilience can be conferred particularly on the population of healthy abused individuals.

2.1.4.5. Conclusions

This is the first study to have found that found cognitive resilience and vulnerability to depression following childhood trauma is reflected in differences in the psychophysiological function of affective modulation. Previously, resilience as an effect of childhood trauma was investigated in personality traits (Wingo et al., 2010b) and various cognitive performances of reasoning and memory (Wingo et al., 2010a). It is interesting that superior nonverbal memory, which is possibly related to the ability to efficiently process emotional information, was found in resilient individuals (Wingo et al., 2010a). Together with the present findings, it underscores the importance of assessing emotional processing in relation to childhood trauma and depressive pathophysiology. The results overall add to the growing body of literature documenting dysfunctional startle modulation linked to depression and highlight affective modulation as a critical property rendering individuals resilient to depression against the potentially adverse effect of childhood trauma. Ability to flexibly respond to emotional variations seems important in maintaining an individual's positive mental health to the extent that it ultimately prevents a negative bias. Such cognitive resilience may protect those individuals from psychiatric problems. Important clinical implications follow from these current findings. In particular, it suggests that a focus of future treatments for depression following childhood trauma should be on the recovery or gaining of normal affective startle modulation in vulnerable individuals. This would provide them with resilience to future symptom recurrence. In fact, there is evidence that psychological

therapies are more effective in treating depressed patients with a history of childhood trauma than are pharmacological therapies (Nemeroff et al., 2003). The development of novel and specifically targeted therapeutic methods aiming to improve affective startle modulation in depressed individuals is warranted for future translational research on depression. Furthermore, the use of objective measures of affective modulation such as those presented in this study could be used as one of the targeted endpoints of therapies, and as an indicator of enhanced longer-term resilience against future depressive symptoms or episodes.

2.2. Experiment 2. Cortisol stress reactivity

Long term effects of childhood trauma on cortisol stress reactivity in adulthood and relationship to the development of depression

Abstract

Background and Aims

Childhood trauma may have longstanding effects on individuals' propensity to react adversely to stress, and also predisposes individuals to suffer from depression. The current study aimed to examine stress reactivity in individuals with and without a history of childhood trauma by measuring cortisol responses to the passive viewing of stressful images, specifically including images relevant to childhood trauma. In addition, participants with and without a diagnosis of current depression were studied to investigate whether cortisol stress reactivity may underlie resilience or vulnerability to depression.

Methods

The study involved 17 healthy participants with and 24 without a history of childhood trauma; and 21 depressed patients with and 18 without a history of childhood trauma. Salivary cortisol was measured before, during and after participants were shown affectively laden images, including standardised scenes from the International Affective Picture System and also images suggestive of childhood abuse. Cortisol stress reactivity to the passive image viewing was compared between groups.

Results

In those who had experienced childhood trauma, cortisol stress responses were overall low and the same in those who were depressed and those who were not (mean stress reactivity variable- depressed: 0.8; non-depressed :0.72). In contrast, cortisol stress reactivity was raised in depressed subjects without a history of childhood trauma (mean stress reactivity variable- depressed: 3.75; non-depressed:0.1).

Conclusions

A history of childhood trauma has longstanding effects on adulthood cortisol responses to stress, in that individuals with a history of childhood trauma show blunted cortisol responses. However, this effect is seen irrespective of whether these individuals become depressed, suggesting that such a finding does not explain subsequent resilience or

vulnerability to depression. On the other hand, patients who experience depression without a history of childhood trauma show enhanced cortisol stress reactivity, which could help explain the aetiology of their depressive illnesses. Differences between the current findings and those using other pharmacological and stress challenge paradigms may relate to the type of stimuli used and to dysfunction at different levels of the HPA axis.

2.2.1. Introduction

In the face of an aversive event, psychological stress generates a cascade of physiological and behavioural responses enabling an organism to adapt to the situation in order to protect itself. The hypothalamic-pituitary-adrenal (HPA) axis is an intrinsic part of the brain response to such stress and underlies many of the cognitive and behavioural manifestations of arousal, alertness and vigilance required to tackle the threat. Immediately after a threatening event is perceived, the hormones of the HPA axis are activated causing an increase in the circulating level of its end product of corticosteroids, which interact with cognitive functions as well as bodily functions of immunity and inflammation (de Kloet et al., 1999; McEwen, 1998). Concentration of the corticosteroid cortisol in humans rises to peak levels after 15-30 min and declines slowly to pre-stress levels 60-90 min later. Cortisol then negatively feeds back to the brain areas that initially activated the HPA axis, achieving homeostasis by eventually terminating the activation of the whole system, as the threat becomes no more imminent (McEwen, 2003).

This homeostasis of the HPA axis can, however, be dysregulated by excessive release of corticosteroids in response to chronic or severe stress (de Kloet et al., 2005). Children's brains, in which development is still ongoing, are particularly vulnerable to such overexposure to corticosteroid. It is hypothesised that via such a mechanism the stressful experiences of childhood trauma could have a long-life adverse effect on the HPA axis functioning, thereby increasing the later risk of psychiatric diagnoses (Heim and Nemeroff, 2001).

That childhood trauma is causally associated with the psychiatric diagnoses of depression is suggested by the high prevalence of depression within abused populations in epidemiological studies (Chapman et al., 2004). Previous neuroendocrinological studies have investigated this relationship by attempting to identify hormonal abnormalities specific to individuals with a history of childhood trauma, which may play a mediatory role between early life stress and depression. Thus, cortisol reactivity to pharmacological challenges such as dexamethasone (Dex) and corticotrophin

releasing hormone (CRH) has been commonly measured to assess HPA axis functioning and its role in this link.

With the use of Dex or Dex/CRH challenge, cortisol responses have been found to be suppressed in healthy individuals with a history of childhood trauma (Klaassens et al., 2009), sexual abuse (Stein et al., 1997) and emotional abuse (Carpenter et al., 2009). However, cortisol responses have been found to remain enhanced in depression (Heim et al., 2008a) and other psychiatric conditions (Faravelli et al., 2010) in those with a history of childhood trauma.

Whilst pharmacological challenges are valid techniques to assess cortisol reactivity, more subtle perturbations such as those related to a history of childhood trauma or to depressive symptomatology may be better examined by using endogenous physiological responses, for example to psychological stresses. Psychological stress often precipitates the onset of and exacerbates the severity of depression, providing ecological validity for such an approach. Different endogenous physiological responses to stress, in the form of cortisol reactivity, may reflect individual differences in susceptibility to depression. Similarly, childhood trauma may have an adverse consequence of dysfunctional HPA axis reactivity which in turn reduces individuals' responses to and ability to cope with subsequent psychological stress in adulthood.

The Trier Social Stress Test (TSST: Kirschbaum et al., 1993), a psychosocial stress challenge in which individuals are asked to make a speech and to perform arithmetic tests in public, has been used to examine individual cortisol responses and hence cortisol stress reactivity. The TSST aims to create a naturalistic situation imposing psychological stress and has been standardised as it has previously been used in many studies that examine individual differences in cortisol stress reactivity.

Previous studies of the TSST on samples with a history of childhood trauma have shown lower cortisol reactivity in healthy adults (Carpenter et al., 2007), both men (Elzinga et al., 2008) and women (Carpenter et al., 2010), but have shown increased responses in depressed women (Heim et al., 2000). Severity of depression, the number of childhood traumas and the number of adulthood traumas have been correlated with the level of increase in cortisol responses (Heim et al., 2002). With a history of

childhood trauma, depressed adolescents have also shown increased responses (Rao et al., 2008), but only when the symptoms are mild (Harkness et al., 2010). In contrast, healthy female adolescents (MacMillan et al., 2009) and healthy children (Ouellet-Morin et al., 2011) show lower responses.

Taking these findings together, cortisol responses may be lower in those who remain well in adulthood despite their experience of early life stress, but higher in those who later develop depression. Thus, it may be that there are differential effects of childhood trauma on cortisol stress reactivity. Childhood trauma may confer on some individuals neuroendocrine resilience in the form of blunted cortisol reactivity protecting against subsequent adulthood stress, and this may prevent them from manifesting psychiatric problems. Childhood trauma may, however, confer on others neuroendocrine vulnerability in the form of enhanced cortisol reactivity to adulthood stress, which may make those individuals more likely to manifest depressive symptoms.

The TSST is the most frequently used experimental paradigm to identify the effect of childhood trauma on cortisol stress reactivity. This paradigm, however, may not be uniformly effective with all individuals because responses can vary depending on individuals' personality traits. Psychosocial stress may particularly be amplified in socially anxious or young individuals. However, it would not have the same effect on individuals who have little fear in performing tasks in public, particularly when the task does not directly involve their personal achievements such as in exams or job interviews. Therefore, results from using this paradigm may not generalise to different sample types.

In order to address this limitation, the current study used a passive image viewing paradigm, aiming to produce a condition that is more generally accepted as stressful in any healthy population. Participants are shown stress-inducing images that are suggestive of scenes of childhood trauma, and negative images chosen from the International Affective Picture System (IAPS:Lang et al., 2005) based on published affective norms. The IAPS is frequently used as material for experimental psychophysiological paradigms measuring the magnitude of eye blinks in response to startle, and its modulation by affective valence of images (Lang et al., 1990). It has successfully been demonstrated that individuals show differential emotional physiological responses to negative versus positive affective valence of images. This

evidence is robust in healthy individuals, suggesting that the level of stress induced by negative images is fairly consistent in general populations (Lang, 1995). Those images are mildly stressful but are valid to the extent that they are perceived as uniformly and sufficiently stressful to activate cortisol stress responses.

The aim of the current study was to determine whether there is any abnormality in the HPA axis, specifically of cortisol stress reactivity elicited by the viewing images related to childhood trauma, that is specific to adults with a history of childhood trauma; and to determine whether any abnormality may moderate the relationship between childhood trauma and depression. A cross-sectional study recruiting four sample groups of healthy and depressed individuals with and without a history of childhood trauma was used to determine the interactive effect of childhood trauma and depression.

The neuroendocrine profile of healthy adults with a history of childhood trauma parallels their resilience to depression, whilst that of depressed adults with the same history parallels their vulnerability to depression. This is the first study that has measured cortisol reactivity to the stress exposure of passive image viewing, and to examine the differential effects of depression and childhood trauma. Based on previous evidence, we hypothesised that resilient individuals would show blunted cortisol responses to stressful images but vulnerable individuals would show the opposite pattern. An interactive effect of childhood trauma and depression would reflect how differently childhood trauma influences cortisol reactivity between resilient and vulnerable individuals and clarify how abnormality in HPA functioning mediates the relationship between childhood trauma and depression.

2.2.2. Methods

2.2.2.1. Participants

Out of the total 83 participants who were recruited for the experimental session, 80 participants completed saliva sample collections. A total of 80 participants (28 males

and 52 females) were analysed into four groups comprising: 17 healthy participants with (H/A) and 24 without (H/NA) a history of childhood trauma; and 21 depressed patients with (D/A) and 18 without (D/NA) a history of childhood trauma. A statistical power analysis was performed for sample size estimation based on data from a published study (Heim et al., 2002), examining correlations between childhood trauma and stress reactivity. The effect size in this study was 0.35. With an alpha = .05 and power = .08, the projected sample size (GPower 3.0.8) is approximately N = 64. Thus our proposed sample size of 80 was more than adequate for the main objective of this study investigating the possible mediatory roles of cortisol stress reactivity between childhood trauma and depression by using mediation analyses.

All depressed patients were either currently admitted to or discharged from a hospital with a diagnosis of Depressive Episode or Recurrent Depressive Disorder using the criteria of International Statistical Classification of Diseases and Related Health Problems (ICD-10). In addition, for a depressive episode to be sufficiently severe to be included required a score above 14 on the Inventory of Depressive Symptomatology (QIDS-SR). All depressed patients were recruited from in- and out-patient facilities of the South London and Maudsley NHS Foundation Trust.

Healthy participants were recruited by advertisement at and around the hospital and university sites. They were required to be free from a personal history of any psychiatric disorder, and to have no psychiatric disorder in first degree relatives.

Additional inclusion criteria for all participants were: age range between 20 and 65 years old; the absence of neurological disorders; and no history of substance misuse within the previous 2 years. Participants were not required to be completely medication free, but medication use that could affect the HPA axis was excluded, with the exception of antidepressant medication in patients which was allowed to be continued for ethical reasons.

The participants were invited to a general health monitoring session prior to the test, and were administered the Childhood Trauma Questionnaire (Bernstein et al., 2003) to assess their experiences of childhood trauma. Those who scored at or above ‘moderate-severe’ level in at least one of the five subscales (emotional abuse (EA), physical abuse

(PA), sexual abuse (SA), emotional neglect (EN) and physical neglect (PN)) of the CTQ were then assigned to the relevant experimental groups (H/A or D/A). Those who scored below the same level were assigned to non-abused groups (H/NA or D/NA).

The study was approved by the National Research Ethics Committee London – London Bridge. All participants provided written informed consent for their participation in the study. They were compensated for their time and travel.

2.2.2.2. Procedure

The test day was scheduled to coincide with days 1 to 10 of the menstrual cycle for pre-menopausal female participants, since HPA reactivity is potentially affected by menstrual cycle phase. On the test day, participants arrived between 12:00 and 14:00. They were asked to refrain from eating for at least 2 hours prior to their visit. Caffeine intake and cigarettes were also prohibited before and during the session. Upon arrival, they were given a short briefing about the experimental sessions and asked to be seated to relax themselves as necessary for at least 10 and up to 30 minutes before the start of the sessions.

Each participant viewed 48 stress-inducing images as well as 48 non-stress inducing images. Stress inducing images comprised 24 negative affect images chosen from International Affective Picture System (IAPS) and 24 images chosen from a public photo archive (www.istockphoto.com) to represent each of four types of childhood trauma (emotional abuse, physical abuse, sexual abuse and emotional neglect; 6 images for each sub-type). Non-stress inducing pictures were 24 positive and 24 neutral images chosen from IAPS. Images were presented in a pseudorandom order.

Participants viewed this set of images in two different experimental sessions. In the first session (session 1), they passively viewed the images projected onto a wall at the same time as their eye blink startle response to the acoustic stimuli of white noise was measured by using electromyogram (EMG). In the second session (session 2), they performed a computerised task to rate the same images displayed on a computer

monitor with respect to their experiences of pleasure, arousal, interest and stress from viewing the images.

In session 1, each image was viewed for 6 sec with the interval between the images varying from 3 to 9 sec. Images were projected onto a blank wall with a size of 60 x 90 cm approximately 2 m in front of participants via a Benq data projector (Model W100).

In session 2, each image was viewed for as long as participants wanted until they pressed a computer key to proceed to the rating questions for that image. They were then asked to rate the image they had viewed within a 9-point likert scale by pressing the number key corresponding to their answer. Four questions asking their experiences of pleasure, arousal, interest and stress followed one by one after the presentation of each image. Image presentation was controlled by the visual-stimuli presentation software SuperLab (Cedrus Corporation, San Pedro, CA 90734 – USA) in a Toshiba Satellite Pro P300-1CV 15-inch laptop computer.

2.2.2.3. Stress measure

Salivary cortisol was measured to investigate the effects of image exposure on HPA axis reactivity. Saliva samples were obtained by passive drool into sterile plastic tubes. Over the course of the sessions, two saliva samples were collected 5 minutes apart on three occasions: before session 1 (S1 & S2), between session 1 and 2 (S3 & S4), and after session 2 9S5 & S6).
Samples were taken straight to the laboratory where they were immediately frozen at – 20 C.

For the subsequent analysis, after thawing, they were centrifuged at 3500 rev/min for 10 min, which resulted in a clear supernatant of low viscosity. Saliva cortisol concentrations were determined using the 'Immulite'- DPC's Immunoassay analyzer (www.diagnositcis.siemens.com). The plasma cortisol assay of the analyzer was suitably modified and then validated for these measurements. A set of 10 cortisol standards in saline were used in each assay to plot a calibration graph. This was highly reproducible with slope (mean+SEM) 0.197+0.004. The method correlated well with a

previously published TR-FIA (Juruena et al., 2006). It had analytical sensitivity of 0.2 nmol/l and inter/intra assay precision (% CV) of less than 10% (cortisol concentration range 5 to 25 nmol/l). All samples from the same participant were analysed in the same run.

2.2.2.4. Self-report assessment

The participants completed a battery of self-report assessments measuring the following current psychological and psychiatric conditions after the completion of the whole session as noted in Table 2.1.1 (See page 63).

2.2.2.5. Statistical analysis

In order to examine cortisol curve over the course of the experimental sessions, a three-way mixed model ANOVA was conducted on mean cortisol levels of the two collections at the three time periods (before session 1 [T1], between session 1 and 2 [T2], and after session 2 [T3]). The two between subject factors were condition (H x D) and childhood trauma (A x NA) and the within subject factor was collection time (T1, T2 & T3). However, this averaging method may have contaminated the magnitude of specific stress responses immediately following the image exposure at session 1. Therefore, we also measured the differences in cortisol levels between pre-exposure and post-exposure to the images (Stress reactivity = S3 – S2) in order to examine more specifically the cortisol response to the first series of images. A two-way ANCOVA was conducted on this stress reactivity variable. The between subject factors were condition (H x D) and childhood trauma (A x NA). The scores of the six self-report assessments administered for anxiety, self-esteem, PTSD symptoms, current stressful events, depressive symptoms, dissociative symptoms, and age were entered as covariates.

In addition, to examine possible mediatory roles of neuroendocrinological function between childhood trauma and depression, mediation analyses were conducted within the variable of childhood trauma (CT: A/NA), current depressive state measured by QIDS-RS (Dep) and stress reactivity.

Additionally, the differential effects of different trauma types were examined by conducting Pearson correlational analyses between the scores on trauma type subscales and the stress reactivity variable. This was undertaken separately in the abused control and abused patient groups.

2.2.3. Results

2.2.3.1. Demographic data

One participant was withdrawn from the study during the experiment and did not complete the second session. She was eliminated from the study and not entered into the analysis. Demographic data for the total of 79 participants after this adjustment are summarized in Table 2.2.1. As is shown, the four groups did not differ with respect to age, gender and the magnitude of recent stressful events. The abused groups (H/A and D/A) had higher mean scores for all CTQ subtype scales than the non-abused groups. As expected, the patient groups both with and without a history of childhood trauma had higher mean scores for the scales measuring current anxiety, PTSD symptoms, depressive symptoms and dissociative symptoms, and lower mean scores for the scale measuring self-esteem than the healthy participant groups.

Table 2. Participant Characteristics

	H/A (n=17)	**H/NA (n=24)**	**D/A (n=20)**	**D/NA (n=18)**	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Statistics
Age (year)	44.29 (12.54)	45.3 (13.72)	52.05 (11.99)	51.72 (10.77)	NS
Gender	M:8, F:9	M:9, F:15	M:4, F16	M:7, F:11	NS
CTQ					
EA	12.2(3.8)	5.9 (1.4)	14.8 (5.1)	6.2 (1.9)	$F(3, 75) = 35.1, p < .001$
PA	10.2 (5.1)	5.3 (.5)	7.9 (4.2)	5.2 (.7)	$F(3, 75) = 10.4, p < .001$
SA	7.5 (3.8)	5.0 (.2)	8.4 (4.8)	5.0 (.2)	$F(3, 75) = 6.6, p < .001$
EN	14.1 (4.3)	6.7 (1.7)	16.8 (4.8)	8.8 (3.1)	$F(3, 75) = 34.0, p < .001$
PN	8.1 (3.2)	5.9 (1.4)	8.5 (3.8)	5.6 (1.0)	$F(3, 75) = 6.3, p < .01$
CTNO	2.2 (1.2)	0	2.3 (1.3)	0	$F(3, 75) = 42.7, p < .001$
ZAS	28.6 (4.7)	28.2 (4.8)	40.7 (8.4)	43.6 (11.1)	$F(3, 75) = 21.6, p < .001$
RSS	22.5 (5.0)	22.7 (4.2)	10.5 (3.9)	10.3 (6.1)	$F(3, 75) = 41.6, p < .001$
SRRS	1.7 (1.0)	1.6 (.9)	1.76(1.0)	1.7 (1.0)	NS
IES-R	19.5 (15.8)	12.5 (11.2)	36.8 (14.4)	38.7 (15.9)	$F(3, 75) = 16.7, p < .001$
QIDS-SR	11.1 (6.3)	5.6 (3.0)	41.1 (14.6)	35.6 (14.9)	$F(3, 75) = 54.2, p < .001$
DES	7.0 (6.7)	4.4 (3.5)	13.3 (13.3)	14.8 (16.6)	$F(3, 75) = 4.1, p < .01$

* Statistics are one-way ANOVAs with a between-subject group factor (H/A, H/NA, D/A and D/NA) on the variables of age, CTQ subtypes, the number of CT (CTNO) and the self-report assessment scores (EA – Emotional abuse, PA – Physical abuse, SA –

Sexual abuse, EN – Emotional neglect, PN – Physical neglect, ZAS – Zung Anxiety Scale, RSS – Rosenberg Self-esteem Scale, SRRS – Social Readjustment Rating Scale, IES-R – The impact of Event Scale Revised, QIDS-SR – Inventory of Depressive Symptomatology, DES – Dissociative Experiences Scale), and chi-square test on gender. NS = non-significant,

2.2.3.2. Cortisol reactivity

Mean salivary cortisol levels for each collection (S1-6) across the four groups are plotted in Figure 2.2.1. It shows a trend of an increase in cortisol levels immediately after Session 1 across the groups, reflecting the participants' stress responses to the emotional images. This is superimposed on a gradual diurnal fall over time.

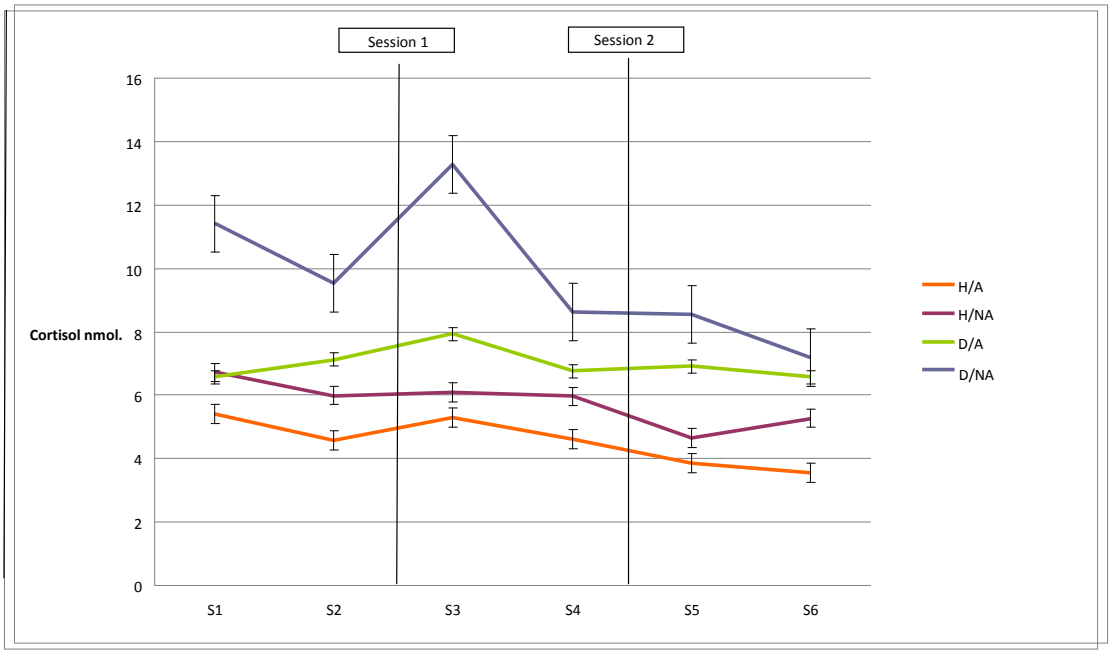


Figure 2.2.1. Observed cortisol (nmol/l) by group over time (S1 = sample 1, S2 = sample 2, S3 = sample 3, S4 = sample 4, S5 = sample 5, S6 = sample 6)

A three-way mixed ANOVA (childhood trauma x condition x collection time) on average cortisol levels of the two collections at the three time periods showed significant main effects of condition ($F(1, 75) = 5.1$, $p < .05$) and collection time ($F(2, 150) = 7.8$, $p < .01$). As is shown in Table 2.2.2., mean cortisol levels were overall higher in depressed individuals than in healthy participants. However, there was neither three-way interaction nor effects relating to childhood trauma.

Table 3.. Mean and standard deviation for average cortisol levels for each time period (nmol/l)

	H/A	H/NA	D/A	D/NA
T1 - before session 1	5.0 (2.83)	6.35 (4.76)	6.84 (4.32)	10.46 (13.97)
T2 - between session 1 and 2	4.95 (2.30)	6.02 (4.30)	7.34 (5.02)	10.94 (12.56)
T3 - after session 2	3.71 (1.19)	4.96 (4.19)	6.74 (4.42)	7.88 (7.04)

A two-way ANCOVA (childhood trauma x condition) with the scores of self-assessments as covariates on the stress reactivity variable (S3 – S2) showed a significant interaction of condition and childhood trauma ($F(68,1) = 4.4$, $p < .05$) as well as a main effect of dissociative symptoms ($F(1,68) = 3.9$, $p = .05$). No main effects of childhood trauma and depression were found. Figure 2.2.2. shows the means of the stress reactivity variable by group. The main finding in relation to the interaction of stress reactivity and group is that stress reactivity is higher in non-abused depressed patients than in all of the other groups. In other words, the enhanced stress reactivity in patients compared to participants was only seen in the non-abused group ($t(41) = 3.68$, $p < .05$). Furthermore, stress reactivity was overall low in those with a history of childhood trauma regardless of the diagnosis and there was no significant difference between healthy participants and depressed patients.

In the mediation analysis, however, there was no significant indirect effect of childhood trauma on current depressive state through stress reactivity.

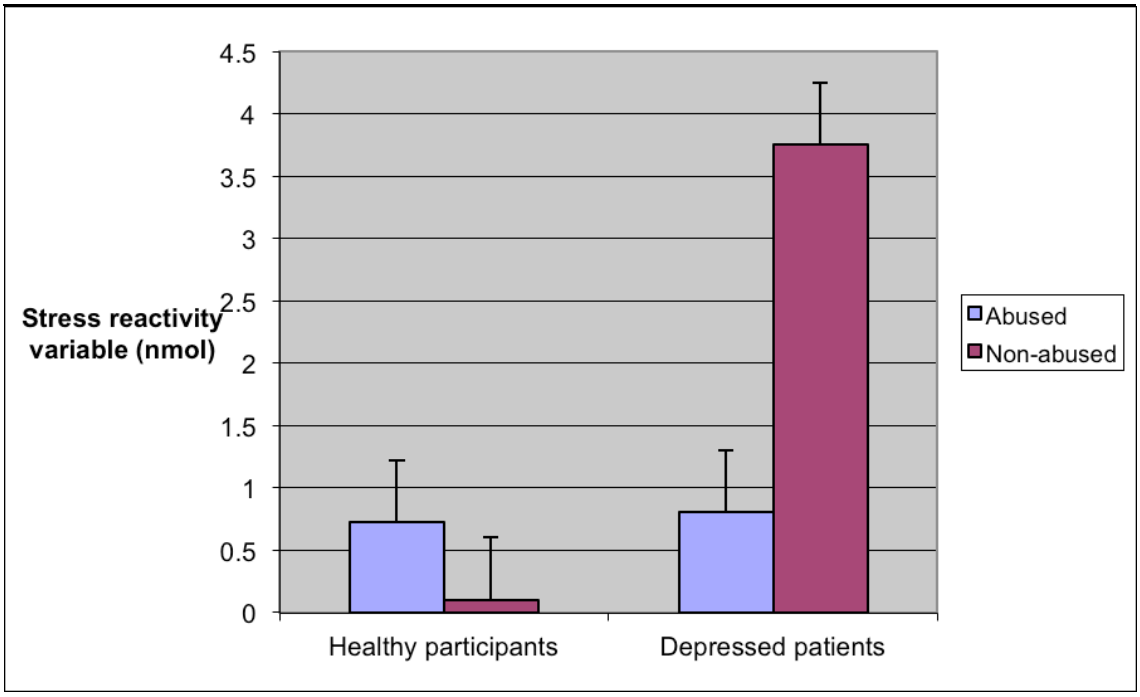


Figure 2.2.2. Means and +1 standard errors of stress reactivity variable (measures as nmol/l increase in salivary cortisol, in which the cortisol value of S2 is deducted from the cortisol value S3) in the four groups.

In multiple correlation analyses between the scores of trauma type subscales and stress reactivity variables, only a significant positive correlation between emotional neglect and stress reactivity ($r = .49$ (18), $p < .05$) was found in the abused depressed patients. There were no correlations in the abused healthy participants.

2.2.4. Discussion

The primary goal of the current study was to investigate the effects of childhood trauma and depression on cortisol reactivity by using a stress-inducing experimental method involving passive viewing of affectively laden images. This is the first study to use such an experimental paradigm as an alternative to the most commonly used paradigm, the TSST, to examine the effect of childhood trauma and depression on cortisol reactivity. The image viewing paradigm was expected to induce psychological stress more effectively than the TSST in individuals with a history of childhood trauma, and to provide more specific information as to individuals' reactivity in response to relevant and ecologically valid stressors in the context of a history of abuse.

2.2.4.1. Main findings

We found a significant interactive effect of depression and childhood trauma on stress reactivity.

The first main finding is that, irrespective of individuals' susceptibility to depression, those with a history of childhood trauma showed a reduced cortisol reactivity to stress. This suggests longstanding effects of such experiences in childhood on later adulthood stress reactivity.

Second, previous studies using the TSST had suggested that within the group who had experienced childhood trauma, those vulnerable to depression have an increased cortisol reactivity to stress compared to those who are not vulnerable to depression. However, we did not find such a relationship using the current experimental paradigm. Instead, it was depressed patients *without* childhood trauma who showed to highest levels of cortisol reactivity. Whilst this contradicts the initial hypothesis, it does nonetheless attest to important differences in the aetiology of depression in those with and without histories of childhood trauma.

Third, we have demonstrated that there are no significant differences in cortisol stress reactivity between healthy and depressed sample groups with a history of childhood trauma. Thus, cortisol responses do not appear to differentiate between those who will and will not develop depression after childhood trauma. In addition, a mediation analysis examining the possible mediatory role of neuroendocrinological function between childhood trauma and depression did not show a significant indirect effect of the former on the latter through cortisol stress reactivity.

Previous studies found enhanced cortisol responses to another laboratory stressor, the TSST, within depressed abused individuals (Heim et al., 2000) but blunted responses to the TSST within healthy abused individuals (Carpenter et al., 2007; Carpenter et al., 2010; Elzinga et al., 2008). These findings have been interpreted as meaning that, amongst those with a history of early life stress, individual differences in resilience and vulnerability to depression could be signified and perhaps mediated by blunted stress cortisol reactivity (resilience) and enhanced stress cortisol reactivity (vulnerability). Thus, the current study which found no differential hormonal characteristics of resilience and vulnerability to depression within a group of subjects with a history of

childhood trauma, did not replicate the previous findings with the use of a different stress-inducing technique (the TSST).

There are several possible explanations for these differences. One may be the difference between the neurobiological effects of passive image viewing and the active participation required in the TSST, in which those different types of stress exposure differentially affect the HPA axis. Furthermore, in the current study a proportion of the images viewed had particular relevance to those who had experienced childhood abuse or trauma, representing a specific type of stress rather than a more generic one.

2.2.4.2. Adrenocortical abnormality in childhood trauma

Our main findings of overall low stress reactivity in those with a history of childhood trauma are comparable to those from a study which used a pharmacological challenge with synthetic adrenocortico-trophin hormone (ACTH) (Heim et al., 2001). This previous study found low cortisol concentrations in response to ACTH stimulation both in depressed and healthy women with a history of childhood trauma. The results implicate low adrenocortical activity within abused populations and suggest childhood trauma has the effect of downregulating adrenocortical function, possibly due to the long term effects of excessive ACTH stimulation. Moreover, this adrenocortical dysfunction is equally expressed in individuals both resilient and vulnerable to depression, and depressive symptoms seem to have no interactive effect on adrenocortical dysfunction to mitigate or exacerbate the symptoms.

2.2.4.3. Differential effects between the passive image viewing paradigm and the TSST

Our results failed to confirm the hypothesis of differential neuroendocrine characteristics of blunted cortisol stress reactivity in healthy abused individuals and enhanced cortisol stress reactivity in depressed abused individuals. However, our findings are similar to those of ACTH challenges in the cross-sectional study design of Heim et al. (2001) using similar sample groups as ours. Our experimental paradigm may,

thus, have an effect that mirrors results from an ACTH challenge but induces a different type of stress reaction from the TSST.

The effect of the passive image viewing as a psychological stressor is still little known as it has been used in only two previous studies. One study made a gender comparison within healthy participants. Cortisol increase was measured immediately after the image viewing in this study and no significant difference between genders was found (van Stegeren et al., 2008). Another study on the effect of cannabis use has shown significant cortisol increases both in cannabis users and non-users after viewing a set of negative images but has shown a significant ACTH increase only in non-users (Somaini et al., 2012). This latter study showing differences between ACTH and cortisol reactivities indicates that the image viewing method may differentially affect the various levels of the HPA axis. It is possible that this particular paradigm of passive image viewing may be more sensitive in detecting alterations in adrenocortical functions than the TSST, which may only be effective in inducing stress reactions that are apparent at a higher level of the HPA axis, for example at a pituitary level or higher.

Another cross-sectional study with the same types of sample groups as we used has also shown differential effects of childhood trauma and depression on ACTH and cortisol reactivity to the TSST (Heim et al., 2000). It has shown ACTH increase in abused individuals regardless of their psychiatric conditions but cortisol increase only in depressed abused individuals. The TSST thus seems more effective for probing enhanced pituitary reactivity but not suppressed adrenocortical reactivity to stress, such as that probed by the current image viewing paradigm. Cortisol secretion is a secondary consequence following ACTH releases from pituitary, and suppressed adrenocortical function as a function of childhood trauma is likely to be masked by overactivation of ACTH in response to stress imposed by the TSST. A significant increase in cortisol responses that is evidenced in the depressed abused individuals in Heim et al's study (2000) can be interpreted as the excessive ACTH releases having overridden suppressed adrenocortical reactivity.

2.2.4.4. Psychiatric comorbidity

Symptoms of PTSD may be a confounding factor in the results. PTSD is commonly comorbid with depression and is also known to induce hypocortisolemia (Yehuda et al., 1995; Yehuda et al., 1990). Since PTSD symptoms were raised in the depressed group, it is possible that comorbidity with PTSD could have influenced the cortisol reactivity in our depressed groups. Indeed, our analyses attempted to control this possible confounding factor using measures of the current severity of PTSD symptoms. However, we had no measure of the past severity of comorbid PTSD, which might also have contributed to functional alterations in the HPA axis. It is therefore possible that variability in the severity of PTSD symptoms could have contributed to reduced cortisol reactivity to the image viewing in the depressed abused group, potentially confounding the hypothesised relationship between abuse, depression and elevated cortisol responses. Our results have, however, shown overall elevated cortisol levels throughout the experimental sessions in the depressed subjects, which is in line with many previous studies demonstrating HPA axis dysfunction in mood disorders. Hypercortisolaemia is a well-documented neuroendocrinological phenomenon in depression (Young, 2004).

2.2.4.5. Methodological limitations

Methodological considerations for this discrepancy between the current and previous findings are summarised as follows.

First, it must be acknowledged that the HPA axis is a complex set of chain reactions of various stress hormones. Since the activities of those stress hormones interact and regulate each other, it is difficult to probe functional alterations at one specific target level at the HPA axis. Unlike the targeted stimulation of a pharmacological challenge, psychological stress, theoretically, only directly affects the highest level of the HPA axis to initiate the release of CRH prior to its subsequent stimulatory activity to the pituitary. Subtle degrees of suppressed reactivity may thus not be adequately detected by many psychological stress-inducing experimental paradigms including the TSST as such abnormality might be overridden by the overactivation of stress hormone at those higher levels.

Furthermore, various experimental paradigms utilising a psychological stressor may cause differential degrees of stress activation that may as a result then reveal disturbances at different levels of the HPA axis. Thus, the TSST might be more

effective in inducing stress reactions at the level of pituitary than the image viewing paradigm that may reveal dysfunction at the lower level of adrenal cortex.
In order to clarify these methodological issues, analyses of the activities of multiple types of stress hormones, not just cortisol but also ACTH and CRF, should be concurrently conducted so that those activities are compared and their differential abnormalities are identified. Effectiveness of experimental methodologies in inducing psychological stress reactions should also be explored and which level of the HPA axis is most affected by each should be clarified.

2.2.4.6. Conclusions

In conclusion, the current study found that a history of childhood trauma has longstanding effects on adulthood cortisol responses to stress, specifically to viewing affectively laden images. Individuals with a history of childhood trauma show blunted cortisol responses. However, this effect is seen irrespective of whether these individuals become depressed, suggesting that such a finding does not explain subsequent resilience or vulnerability to depression. On the other hand, patients who experience depression without a history of childhood trauma show enhanced cortisol stress reactivity, which could help explain the aetiology of their depressive illnesses. This attests to significant differences in the origins and development of depression between those who have and have not experienced childhood trauma.

2.3. Experiment 3: Facial emotion recognition

Processing bias of facial emotions as a function of childhood trauma: resilience and vulnerability to depression

Abstract

Background

There is a high prevalence of depressive symptoms among adults with a history of childhood trauma. A negative cognitive bias is implicated in the aetiology of depressive symptomatology and has also been found within physically abused children, who show preferential processing of anger. However, how these biases mediate the causal link between childhood trauma and adult depression has not yet been clarified.

Methods

The study involved 18 healthy abused and 22 healthy non-abused participants, and 19 abused and 17 non-abused patients. They completed a facial emotion recognition task to assess their efficiency in processing a variety of emotions.

Results

Healthy individuals with a history of childhood trauma made significantly more errors in recognising negative emotions (fear, anger and sadness) but fewer errors in recognizing positive emotion (happiness) than those without childhood trauma. An opposite pattern was found in the group of depressed patients, where those with a history of abuse made fewer errors in recognizing negative emotions. In addition, the severity of physical abuse was positively correlated with the speed to process anger in healthy individuals with a history of childhood trauma.

Conclusions

Resilient individuals – those with a history of childhood trauma but not depression – display positively-biased emotion recognition, which we suggest helps explain why they do not manifest depressive symptoms despite their early experiences of childhood trauma. In contrast, other individuals who become vulnerable to depression after childhood trauma show an amplified bias towards negative emotion. Thus, these enduring individual differences in emotional processing may differentially influence the pathogenesis of depression as a function of childhood trauma.

2.3.1. Introduction

Facial expressions are one of the most fundamental stimuli human beings use to understand others' emotional states and intentions. The ability to quickly capture facial emotions is thus crucial for us when communicating with others and a lack of this ability can cause a serious disturbance in social interactions and interrelationships. This ability to recognise facial emotions has been assessed for altered emotional processing which is implicated in the development and maintenance of depression.
In behavioural experiments, variations of face stimuli categories, of the length and methods of face stimuli presentation, and of task demands were manipulated in order to verify this altered emotional processing in depression (Bourke et al., 2010). Among these task varieties, an identification task in which participants are asked to label facial emotions with given semantic emotional categories has frequently been used due to its simple task demand. Accumulated studies using this method have provided evidence that indicates abnormality of facial emotion recognition within depressed populations.

Initially when the accuracy of the number of correct responses was analysed, general impairment of emotion recognition irrespective of emotional categories in depressed patients was reported (Persad and Polivy, 1993), although their impairment remained more subtle than that of psychotic patients (Archer et al., 1994; Feinberg et al., 1986). Later, different emotional categories started to be taken into account. Depressed individuals were then found to respond to the particular emotional category of sadness less accurately for a subconscious presentation of 80-100ms (Mikhailova et al., 1996; Surguladze et al., 2004) and more slowly (Gollan et al., 2008) and with more misattributions of neutral expressions to sadness (Gollan et al., 2008) compared to healthy individuals. However, at a longer presentation of face stimuli at 200-2000ms, reduced accuracy for processing of more neutral (Leppanen et al., 2004) or happy expressions (Surguladze et al., 2004), but not the negative emotion of sadness, was shown in depressed individuals compared to healthy individuals.

This accumulated evidence overall suggests negatively biased information processing in which a depressed individual shows relative preference of allocating their attention to

negatively valenced stimuli. Slower reaction time to sad expressions in depressed individuals may be caused by an individual's tendency to dwell on those stimuli, which is suggestive of a negative bias. Slower categorisation of sad facial expressions in depressed individuals (Gollan et al., 2008) and with the neurochemical effect mimicking depressed mood in healthy individuals (Harmer et al., 2001) is consistent with this theory, particularly when participants are allowed to view the stimuli as long as they like until they press a name key. With respect to accuracy, the results became slightly inconsistent but some studies indeed clearly have shown a negative bias. For example, with depressive mood, an individual labels positive or neutral stimuli as more negative (Gollan et al., 2008) and that reduces accuracy in responding to positive stimuli (Leppanen et al., 2004; Surguladze et al., 2004). A negative bias also seems to be reversed by antidepressants with reduced accuracy for negative stimuli of fear expressions (Bhagwagar et al., 2004), and increased by acute tryptophan depletion with reduced accuracy for positive stimuli of happy expressions (Hayward et al., 2005). However, subconscious processing with a short presentation of stimuli does not seem to facilitate a negative bias, which is suggested by reduced but not increased accuracy for sadness in depressed individuals (Mikhailova et al., 1996; Surguladze et al., 2004).

In the current study, this identification task is used to examine individual differences of facial emotion recognition in a cross-sectional study design employing healthy and depressed individuals with and without a history of childhood trauma. Epidemiological studies show a remarkably high proportion of depressed individuals report having experiences of childhood trauma (Kessler et al., 1997). Altered emotional processing of the negative bias observed in depressive symptoms may mediate this causal relationship between childhood trauma and depression. Previous studies suggest physically abused children show preferential processing of the particular emotion of anger (Pollak, 2003). However, this is not examined in relation to depressive symptomatology since the child samples used for those studies are not known to be susceptible to depression later in their life. Moreover, this sample bias to physically abused children makes it difficult to examine not just the effect of childhood trauma as a whole but also the differential effects of different trauma types on individuals. The current study addresses these limitations by using depressed adults retrospectively reporting their experiences of childhood trauma and by analysing the differential effects of multiple trauma types scored by Childhood Trauma Questionnaire (CTQ:Bernstein and Fink, 1998).

The current study will use a cross sectional study design,. Specifically, it will examine how childhood trauma affects the negative bias in facial emotion recognition in people with depressive symptoms. Moreover, it will identify individual differences of resilience and vulnerability to depression within the sample groups of both healthy and depressed individuals with a history of childhood trauma. Processing styles of facial emotion specific to the individuals who continue to be healthy against the potentially damaging effect of childhood trauma most likely reflects their resilience to depression, as opposed to those who have experiences of childhood trauma and are later diagnosed with depression. It is hypothesized that while depression-resilient individuals would show a positive bias, depression-vulnerable individuals would show a negative bias. Whether the anger bias noted in earlier studies in physically abused children could be observed in the current adult sample is of another interest. If observed, it would verify whether the behavioural trait of anger bias would persist into adulthood and influence the pathogenesis of depression.

2.3.2. Methods

2.3.2.1. Participants

Out of the total 83 participants, 76 participants completed this experiment of facial emotion recognition. 29 males and 47 females were analysed in four groups comprising 18 healthy abused (H/A) and 22 healthy non-abused participants (H/NA), and 19 abused (D/A) and 17 non-abused patients (D/NA). A statistical power analysis was performed for sample size estimation based on data from a published study (Heim et al., 2002), examining correlations between childhood trauma and stress reactivity. The effect size in this study was 0.35. With an alpha = .05 and power = .08, the projected sample size (GPower 3.0.8) is approximately N = 64. Thus our proposed sample size of 76 was more than adequate for the main objective of this study investigating the possible mediatory roles of facial emotion recognition between childhood trauma and depression by using mediation analyses.

All depressed patients were either currently admitted to or discharged from a hospital with a diagnosis of Depressive Episode or Recurrent Depressive Disorder using the criteria of International Statistical Classification of Diseases and Related Health Problems (ICD-10). In addition, for a depressive episode to be sufficiently severe to be included required a score above 14 on the Inventory of Depressive Symptomatology (QIDS-SR). All depressed patients were recruited from in- and out-patient facilities of the South London and Maudsley NHS Foundation Trust.
Healthy participants were recruited by advertisement at and around the hospital and university sites. They were required to be free from a personal history of any psychiatric disorder, and to have no psychiatric disorder in first degree relatives.
Additional inclusion criteria for all participants were: age range between 20 and 65 years old; the absence of neurological disorders; and no history of substance misuse within the previous 2 years. Participants were not required to be completely medication free, but medication use that could affect the HPA axis of hormonal system was excluded, with the exception of antidepressant medication in patients which was allowed to be continued for ethical reasons.

The participants were invited to a general health monitoring session prior to the experiment, and completed the Childhood Trauma Questionnaire (CTQ :Bernstein and Fink, 1998) to assess their experiences of childhood trauma. Those who scored at or above 'moderate-severe' level in at least one of the five subscales (emotional abuse (EA), physical abuse (PA), sexual abuse (SA), emotional neglect (EN) and physical neglect (PN)) of the CTQ were then assigned to the abused groups (H/A or D/A). Those who scored below the same level were assigned to non-abused groups (H/NA or D/NA). The study was approved by the National Research Ethics Committee London – London Bridge. All participants provided written informed consent for their participation in the study. They were compensated for their time and travel.

2.3.2.2. Task procedure

All participants performed a computerised facial emotion recognition task. The task consisted of 100 pictures of male (n=4) or female (n=4) faces expressing happy, sad, neutral, fearful and angry emotions. Stimuli were selected from gradually morphed

Ekman faces (Ekman, 1976) representing 25% emotion for neutral faces and 100% emotion for all other emotion faces. Each emotion was displayed 20 times ordered pseudo-randomly to avoid repetition of a particular emotion. Presentation was programmed by using the visual-stimuli presentation software SuperLab (Cedrus Corporation, San Pedro, CA 90734 – USA) in a Toshiba Satellite Pro P300-1CV 15-inch laptop computer.

The participants were asked to label the presented face with a semantic category of emotion by pressing one of five coloured keys corresponding to each emotion located in the right hand side corner of the computer keyboard with their dominant fingers as fast as they could. The key to the combination of the colours and emotions was placed on the upper keyboard so that the participants were reminded of the combinations at anytime required. Each face was presented until the participants responded by pressing the key for their choice of emotion. Responses and reaction time was recorded in the SuperLab software.

2.3.2.3. Self-report assessment

The participants completed a battery of self-report assessments measuring the following current psychological and psychiatric conditions after the completion of the facial emotion recognition task as noted in Table 2.1.1. (See page 63).

2.3.2.4. Statistical analysis

For demographic data, one-way ANOVAs with a main factor of group (H/A, H/NA, D/A and D/NA) was conducted on the variables of age, CTQ subtypes (EA, PA, SA, EN and PN) the number of CT and the self-report assessment scores (anxiety, self-esteem, current stressful events, PTSD symptoms, depressive symptoms and dissociative symptoms).

Reaction time (RT) for correct responses, the number of errors (ER) and the number of misattribution biases (MB) for each facial expression emotion (happy, fearful, sad and angry faces) were computed and analysed as outcome variables. For ER scoring, for

example, when a sad face was incorrectly labelled as a fear face, one ER was applied for both sad and fearful emotion misidentification. For MB scoring, when a sad face was incorrectly labelled as a fearful face, one MB was applied only for the fearful face. MB and ER, but not RT, met the kurtosis criteria of normality. RT was subsequently transformed to a logarithmic scale to achieve a normal distribution for further analysis.

To examine possible mediatory roles of facial emotion recognition between childhood trauma and depression, mediation analyses were conducted within the variable of childhood trauma (CT: A/NA), current depressive state measured by QIDS-RS (Dep) and various outcome variables of facial emotion recognition (RT, ER and MB with each emotion type: Happy, Fear, Sad and Angry).

In addition, in order to examine the effect of childhood trauma and depression, a three-way 2 (Group: H x D) x 2 (Abuse: A x NA) x 4 (Emotion types: Happy, Fear, Sad and Angry) ANOVA was conducted on the above three outcome variables.
In order to examine differential effects of different trauma types, Pearson's Product-Moment correlations were also conducted between the scores of each CTQ subscale (emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect) and those outcome variables. These additional analyses and results are presented in Appendix 3.

2.3.3. Results

2.3.3.1. Demographic data

Four out of 76 participants who completed the study had extremely low accuracy (less than 4 correct responses for 20 faces) for fear. These poor performances were considered to reflect the participants' failure in following the task instruction and were then excluded. In addition, an outlier who had particularly been slow to respond (longer than 5000ms for all emotions) and was considered likely to produce a false positive significant correlation (Type 1 error), was excluded.

Demographic data for the total of 71 participants after this adjustment are summarized in Table 2.3.1. The results of one-way ANOVA analyses between the four groups found that they did not differ with respect to age and the magnitude of recent stressful events. The results of chi-square test between the four groups found they did not differ with respect to gender. The abused groups (H/A and D/A) had higher mean scores for all CTQ subtype scales than the non-abused groups. As expected, the patient groups both with and without abuse had higher mean scores for the scales measuring current anxiety, PTSD symptoms, depressive symptoms and dissociative symptoms, and lower mean scores for the scale measuring self-esteem than the control groups.

Table 2 Participant Characteristics

	H/A (n=15)	**H/NA (n=20)**	**D/A (n=19)**	**D/NA (n=17)**	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Statistics
Age (year)	45.94 (11.19)	45.3 (14.39)	50.78 (12.4)	52.29 (10.52)	NS
Gender	M:7, F:8	M:8, F:12	M:4, F15	M:6, F:11	NS
CTQ					
EA	12.4(3.4)	5.8 (1.4)	14.4 (5.6)	6.4 (1.9)	$F(3, 67) = 28.0, p < .001$
PA	9.8 (4.6)	5.3 (.5)	7.8 (4.4)	5.1 (.2)	$F(3, 67) = 8.6, p < .001$
SA	7.7 (4.0)	5.1 (.2)	8.7 (5.6)	5.1 (.2)	$F(3, 67) = 5.3, p < .01$
EN	13.9 (4.4)	6.8 (1.8)	16.4 (4.9)	8.7 (3.1)	$F(3, 67) = 27.1, p < .001$
PN	7.7 (3.1)	5.9 (1.5)	8.1 (3.5)	5.5 (.8)	$F(3, 67) = 4.7, p < .01$
CTNO	2.2 (1.2)	0	2.1 (1.3)	0	$F(3, 68) = 35.8, p < .001$
ZAS	28.8 (5.0)	27.8 (4.8)	40.1 (9.1)	42.7 (11.6)	$F(3, 67) = 15.7, p < .001$
RSS	22.4 (5.3)	23.4 (4.3)	10.9 (4.7)	11.3 (7.0)	$F(3, 67) = 29.2, p < .001$
SRRS	1.8 (1.1)	1.7 (1.0)	1.7 (1.1)	1.8 (1.0)	NS
IES-R	19.7 (16.6)	11.3 (11.4)	34.3 (15.5)	38.8 (15.9)	$F(3, 67) = 13.7, p < .001$
QIDS-SR	10.6 (6.5)	5.4 (3.0)	38.3 (16.4)	34.2 (16.6)	$F(3, 67) = 33.7, p < .001$
DES	5.7 (4.7)	3.9 (2.5)	13.8 (13.4)	14.4 (17.2)	$F(3, 67) = 4.3, p < .01$

Statistics are one-way ANOVAs with a between-subject group factor (H/A, H/NA, D/A and D/NA) on the variables of age, CTQ subtypes, the number of CT (CTNO) and the self-report assessment scores (EA – Emotional abuse, PA – Physical abuse, SA – Sexual abuse, EN – Emotional neglect, PN – Physical neglect, ZAS – Zung Anxiety Scale, RSS – Rosenberg Self-esteem Scale, SRRS – Social Readjustment Rating Scale, IES-R – The impact of Event Scale Revised, QIDS-SR – Inventory of Depressive Symptomatology, DES – Dissociative Experiences Scale), and chi-square test on gender. NS = non-significant,

2.3.3.2. Emotion Processing Task

Means and SD for the all outcome variables (RT, ER and MB) are tabulated in Table 2.3.2.

Table 3 Means and standard diviations for the three outcome variables for each emotion type

	H/A (n=15)	H/NA (n=20)	D/A (n=19)	D/NA (n=17)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Happy ER	1.67 (1.29)	2.45 (2.58)	2.53 (2.44)	1.47 (1.18)
Sad ER	7.27 (3.75)	5.65 (3.73)	7.00 (3.57)	7.88 (4.24)
Fear ER	8.07 (4.03)	6.15 (4.89)	6.95 (4.03)	7.94 (5.26)
Angry ER	5.80 (3.82)	5.05 (3.71)	5.79 (3.61)	6.35 (3.53)
Happy MB	1.27 (1.16)	1.75 (2.61)	1.74 (2.58)	0.76 (0.90)
Sad MB	2.53 (1.81)	1.55 (1.76)	1.47 (2.20)	1.94 (1.92)
Fear MB	4.80 (3.05)	3.60 (3.05)	4.05 (1.96)	5.12 (4.14)
Angry MB	3.13 (2.80)	2.15 (2.70)	3.16 (2.93)	2.53 (1.74)
Happy RT (ms)	2144 (370)	1933 (403)	2461 (903)	2392 (782)
Sad RT (ms)	2788 (498)	2815 (939)	3248 (1066)	4043 (1236)
Fear RT (ms)	3130 (1255)	2876 (1287)	3668 (1574)	4318 (2312)
Angry RT (ms)	2514 (671)	2268 (722)	2696 (1009)	3086 (1408)

In the main mediation analyses, no significant indirect effects of childhood trauma on depression were found through any of the variables examined. Additional analyses are presented in Appendix, showing a significant interaction of group (A/NA), condition (H/D) and emotion types (happy, sad, fear and angry) on ER by using a mixed ANOVA.

2.3.3.3. Response-speed trade-off

Finally a correlation between the total number of correct responses and the mean RT of both correct and incorrect responses across all emotions was conducted. This was undertaken to examine whether it could be the case that the participants who responded incorrectly did so because they made an over-hasty response without allowing sufficient time to make correct judgments. In fact, there was a significant positive correlation between those variables ($r = .36$, $DF = 70$, $p < .01$), suggesting the participants were slower to respond when they were incorrect, thus, there was no speed-response trade-off that may have confounded the results.

2.3.4. Discussion

The primary goal of this study was to examine the effect of childhood trauma on the abnormality of facial emotion processing in depressive symptomatology. By employing four sample groups of healthy and depressed individuals with and without a history of childhood trauma into a cross-sectional study design, interactions of childhood trauma and depression in emotion processing styles were examined. In addition, the current study examined the differential effects of different trauma types on facial emotion recognition by analysing correlations between the scores of CTQ subscales and the variables representing the efficiency of processing facial emotions.

The main findings of the study were as follows;

1) There was no indirect effect of childhood trauma on current depressive state through the mediatory role of facial emotion recognition.
2) The analysis of errors yielded a significant interaction of the three variables of childhood trauma, depression and emotion types displayed in facial stimuli.
3) Significant positive correlations were found between the scores of emotional abuse and the errors on and the reaction time of processing fear in abused healthy individuals.
4) A moderate positive correlation was found between the scores of physical abuse and the reaction time of processing anger in abused healthy individuals.
In the current study, significant interactive effects of childhood trauma and depression were not found on some outcome variables such as reaction time and misattribution bias.

In the current analyses, the errors were scored for one particular emotion in the cases that that emotion is misattributed for other emotion as well as other emotions are misattributed for that emotion. Such a scoring system can assess the level of ambiguity of mental emotional categories an individual retains to use to identify facial expressions. When an individual has a fragile schema of a particular facial emotion in his or her mind, the individual could misattribute this emotion to other emotions as well as misattribute other emotions to this emotion. The errors used in the current analysis thus express the strength of the schema of a facial emotion that may have been developed

through childhood experiences, and that influences individual differences of efficiency in facial emotion recognition.

Possible mediatory roles of facial emotional recognition in which a specific style of facial emotion recognition acquired through childhood trauma could have an effect to exacerbate the severity of depression were not however identified in the current results. Alternative analyses examining interactions of the effect of childhood trauma and depression on errors, however, yielded some results indicating this possible role although it was not theoretically confirmed by mediation analyses.

In the additional analyses results, however, the significant interaction revealed that healthy abused individuals had had less error on a positive emotion but more errors on negative emotions relative to their non-abused counterparts. This suggests that the mental categories for a positive emotion of happiness are less ambiguous than those for negative facial emotions such as anger, sadness and fear in this particular population. These individuals who have experiences of childhood trauma but never suffered from depression in their life signify their resilience to depression. Healthy abused individuals' strong schema of positive facial emotions producing only a few errors on happy expressions may therefore be a key cognitive resilience that may prevent them from developing depressive symptoms against a potentially damaging effect of childhood trauma.

In contrast, in the current results, depressed abused individuals have shown an opposite pattern of errors to that of the resilient individuals. They had more errors on a positive emotion but fewer errors on negative emotions relative to their non-abused counterparts. This suggests the mental categories for the positive facial emotion are more ambiguous than those for the negative facial emotions within abused individuals who have been diagnosed with depression and may have been predisposed as vulnerable to depression.

A negative bias is suggested as the main symptomatic feature of depression as it is evidenced by numerous studies using a variety of experimental measures on depressed patients (Beck, 1967; Bradley et al., 1995; Murphy et al., 2001; Murphy et al., 1999). The weak schema of the positive facial emotion in abused depressed individuals is an intriguing cognitive element composing this negative bias. When an individual's

positive mental categories are so ambiguous that she fails to probe a positive cue in others' expressions, she falls into perceiving her current situation more negatively than it actually is. This maladaptive thought process would generate a symptomatic negative bias. While facial emotion recognition is a requisite skill for human communications, impairment of this skill, reflecting fragile positive schema, can play a critical role in the development of negative bias and hence of depression.

Moreover, this weak positive schema appears to be exacerbated by stress exposure in childhood, as depressed abused individuals made more positive errors than their non-abused counterparts. Childhood trauma can thereby enhance the negative bias, and vulnerable individuals may consequently endure more risk of developing depression than those without a history of childhood trauma. This is, however, not the case for resilient individuals, and similar childhood experiences do not seem to always bring the same psychiatric outcome of depression to individuals with different predispositions.

The current study also examined the differential effects of different trauma types on facial emotion recognition. There were some significant correlations between a number of trauma subtypes and some outcome variables only in abused healthy individuals but not in abused depressed individuals. These significant correlations suggest absence of oversensitivity to negative facial emotions as a cognitive resilience that may have prevented abused healthy individuals from developing depression. Emotional abuse was correlated with a number of outcome variables relating to fear, demonstrating slower and more incorrect responses to fearful expressions as the scores of this trauma type become higher. This suggests that a particular type of childhood trauma, emotional abuse, may confer on an individual insensitivity or the ability to efficiently ignore a negative emotion of fear, preventing their negative bias and maintaining their positive psychological environment.

The scores of physical abuse, however, were only moderately but positively correlated with speed to recognise angry expressions, which contradicts previous evidence of an anger bias within physically abused children (Pollak, 2003). The individuals who scored high in a subscale of physical abuse but have not manifested depression have shown slow responses to anger in the current study but did not show the efficient responses to anger that previous studies yielded. The reason such conflict is apparent between the

current and the previous studies may be the sample age difference or that the latter did not analyse the effect of childhood trauma separately for individuals' resilient and vulnerable predispositions. Children's adaptive behaviour of swiftly recognising others' anger to protect themselves from imminent danger of physical assaults may only be expressed within those individuals who are young or vulnerable but not within those who are grown resilient to depression. Automatic attention to anger led by such oversensitivity is beneficial in an abusive environment but not so in a safe environment in which the expressions of anger are rarely present (Dodge et al., 1995). In an anger-free environment, the anger bias may make an individual wrongly understand others' motivation as harmful although others have no such intentions in reality. Oversensitivity to anger is, in this context, maladaptive and is most likely to lead to the disturbance of subsequent social interactions and interrelationships. Psychological damages from such adverse social outcome are in fact common triggers for the development of depressive symptoms (Farmer, 2002; Lewinsohn et al., 1994). Emotionally and physically abused adults' ability to efficiently ignore negative facial emotions may thus be vital to maintaining the balance between positive and negative emotional responses, and hence to preventing the development of depression.

In conclusion, the current study has identified the differential effects of childhood trauma on facial emotion recognition in populations that are resilient and vulnerable to depression. While resilient individuals show a positive bias in which they make relatively a few errors on happy expressions, vulnerable individuals show a negative bias in which they make many errors on the same expressions as hypothesized. In addition, a number of differential effects of different trauma types have been found on the negative emotions of anger and fear. However, an anger bias was not found in physically abused adults as it may be the cognitive feature only specific to those adults who are predisposed as vulnerable to depression or to children who has not yet developed cognitive control over maladaptive responses to anger.

There is however a limitation in our interpretations of the current results to claim differential effects of childhood trauma on resilient and vulnerable individuals' facial emotion recognition. Since the effect of childhood trauma was examined in adult samples in the current study, it is not known whether the differential emotional responses of the positive bias and the negative bias have been genetically predisposed or

environmentally acquired through the experiences of childhood trauma. An interactive effect of genes and an environmental factor of childhood stress have recently been implicated for the development of depression (Caspi et al., 2003; Ritchie et al., 2009). It is therefore in need to verify whether the identified cognitive vulnerability would have developed in individuals who are genetically vulnerable but only when they are exposed to childhood trauma. Future prospective studies in which facial emotion recognition is assessed at the two stages of pre- and post-trauma together with an individual's susceptibility to depression will be warranted for this clarification.

General discussion

3.1. Summary of main findings

The main aim of the current study was to identify the functional mechanism of altered emotional processing that may play a mediatory role in the causal relationship between childhood trauma and clinical depression, or a resilience to it, in adulthood. This was attempted by using three different experimental measures: (i) affective modulation of the startle response by standard pleasant and unpleasant as well as trauma-relevant pictures, relative to affectively neutral pictures, (ii) cortisol stress reactions, and (iii) facial emotion recognition. This use of concurrent multiple experimental measures made it possible to assess altered emotional processing from the different perspectives of psychophysiology, neuroendocrinology and behavioural psychology, independently as well as in integration. It is particularly important that startle and cortisol responses were measured in parallel so that both responses were considered in the same framework of functional mechanisms.

Above all, resilience and vulnerability to depression as a function of childhood trauma was of particular interest in this project and analysed by comparisons between healthy and depressed groups with a history of childhood trauma. By doing so, the current study aimed to contribute to further understandings of the effect of childhood trauma on individual differences in developmental pathways to psychopathology.

Main Findings

Startle measure:

1) Normal affective modulation, in which startle responses are modulated by a variety of emotional contexts displayed in the images, was found in healthy individuals. The pattern of this modulation, with a particularly strong negative potentiation, was identified as a resilience factor within healthy abused

individuals. While early attentional processing – in which startle responses were suppressed by emotional impacts of the foreground images – was equally intact for the both healthy and depressed individuals with a history of childhood trauma, only the healthy individuals showed normal affective modulation.

2) Affective modulation was compromised in depressed individuals regardless of the history of childhood trauma. Inability to flexibly respond to different emotions shown in the absence of affective modulation may be the element responsible for a negative bias linked to later development of depression.
3) Suppressed startle amplitudes regardless of emotional content of the images were found to mediate the relationship between childhood trauma and current depressive state.

Cortisol measure

1) Contrary to my hypothesis of cortisol hyperreactivity and hyporeactivity in vulnerability and resilience to depression, respectively, there were no differences between cortisol reactivity to emotional images within depressed and healthy individuals with a history of childhood trauma. There was no significant indirect effect of childhood trauma on current depressive state through cortisol reactivity to stress either.
2) Abused individuals showed overall low cortisol reactivity to emotional images regardless of presence or absence of clinical depression.

Facial emotion recognition measure

1) Healthy abused individuals showed more errors on negative facial emotions such as anger, sadness and fear, and fewer errors on positive facial emotion of happiness than healthy non-abused individuals. Depressed individuals showed an opposite pattern. This suggests that positive bias is a form of cognitive resilience that renders abused individuals resistant to depression as opposed to the negative bias that renders those individuals more likely to manifest depression. Childhood trauma has differential effects on emotional processing biases for different predispositions of resilient and vulnerable individuals. However, these effects were not confirmed by mediation analyses of facial

emotion recognition in the relationship between childhood trauma and current depressive state.

A main conclusion drawn from these findings is that the differences between resilience and vulnerability to depression were only evident at behavioural levels but not at hormonal levels of cortisol reactivity. This failure to identify hormonal resilience and vulnerability to depression may be explained in that the HPA axis reacts to stress independently from cognitive stress reactions. Thus hormonal correlates of resilience could not be identified in the current results, in contrast to the strong negative potentiation in affective startle modulation which was found as factor associated with cognitive resilience to depression.

3.2. Resilience and vulnerability – startle affective modulation

The normal, or indeed strengthened affective modulation shown in the startle responses of healthy individuals with a history of childhood trauma reflects their greater capacity to respond differentially to emotional contexts. This emotional responsiveness may be the functional mechanism of cognitive resilience that prevents the development of the negative bias often observed in depressive conditions.

The negative bias in depression is characterised by preferential processing of negative emotive stimuli at a relatively long exposure (Gotlib et al., 2004). For example, this selective orientation to negative stimuli is explained in the comparisons between anxiety and depression. Anxiety is related to automatic attention to the negative and threatening stimuli, whereas depression is related to conscious strategically directed attention to the same stimuli (Mathews and MacLeod, 2005).

A normal pattern of affective modulation is known to emerge only in this late processing at the probe condition of 2000ms or more after the picture onset (Bradley et al., 2006). A number of previous studies (Dichter and Tomarken, 2008; Dichter et al., 2004; Kaviani et al., 2004; Mneimne et al., 2008) as well as the current study have demonstrated that normal startle potentiation to negative stimuli in this late processing is compromised in depressed individuals. Emotional deficits of depression are thus

considered to derive from dysfunctional late processing, namely the absence of negative startle potentiation. The association between this startle deficit and the impairment in strategic controls over attention, for example, may be explained in an interaction of the two systems of affective modulation and attention. In a startle experimental measure, normally, attention affects only early processing by modulating startles in such that attention towards foreground images suppresses the following auditory probed startles (Bradley et al., 2006). However, in depressed individuals, this attention extends to affect late processing. It suppresses auditory probed startles even following long exposure of negative stimuli. Strong conscious attention biased towards negative stimuli, in this case, overrides the threat-protective mechanism of startles that normally should produce negative potentiation. Affective modulation is, then, compromised, suggesting the overpowering effect of conscious attention biased towards negative stimuli. This then leads to a loss of balance in the interactions between attention and affective modulation.

In contrast, affective modulation is intact in healthy individuals with a history of childhood trauma, suggesting their normal threat-protective startle mechanism is preserved. Ability to flexibly allocate conscious attention to different emotional contexts thus protects normal affective modulation, which is expressed as cognitive resilience to depression. This interpretation of the association of attention and affective modulation needs to be confirmed by further studies that examine whether conscious orientation to negative stimuli can interfere with startle negative potentiation, to clarify functional interactions of both. However, the identified superior affective modulation is one of the crucial cognitive expressions of resilience to depression that reflects the ability to flexibly divert attention away from a negative element of life, ultimately preventing the negative bias.

3.3. Resilience and vulnerability – cortisol reactivity

Previously, the relationship of cortisol and emotional processing was studied by examining the effect of exogenous cortisol administration on face processing (Putman et al., 2007a; Putman et al., 2007b, 2010; Taylor et al., 2011), working memory with distracters of emotional images (Oei et al., 2009), self-reports of negative affect (Wirth et al., 2011), and long-term memory of emotional images (Buchanan and Lovallo, 2001).

Cortisol was then found to have the effect of facilitating avoidance of threatening stimuli only when they are used as distracting stimuli (Putman and Roelofs, 2011). Interestingly, exogenous cortisol administration did not have any effects on normal affective modulation of startle responses (Buchanan et al., 2001).

Exogenous cortisol administration is, indeed, not directly comparable with endogenous cortisol reactions in response to stress. Endogenous stress reactions are initiated at the hypothalamus which is the highest level of the HPA axis whose activations ends to induce peripheral cortisol releases. In contrast, exogenous cortisol administration mimics the condition in which cortisol acts to terminate these hypothalamic activations and to restore normal emotional processing in the aftermath of stress reactions. Activation of threat-avoidant behaviours may be specific to this recovery process, which differs from initial stress reactions assessed in the current cortisol study. However, Buchanan's evidence (2001) showing an absence of the effect of cortisol administration on normal affective modulation is in line with the current results. Both Buchanan's evidence and the current results reveal that hormonal activities and emotional processing are distinct in the way they are expressed, but this may be because their interactions are too complex to show a simple one-to-one correspondence.

A methodological limitation explaining this failure to identify hormonal-cognitive associations is also considered in the current measure of hormonal stress reactivity. It is possible that, given the complexity of the HPA axis, the current experimental method did not adequately probe hormonal stress reactivity with sufficient subtlety to differentiate between states of resilience and vulnerability. The current experimental method of image exposure is considered relatively mild, though it should uniformly be perceived stressful to any healthy populations. This is supported by the consistent evidence of the affective modulation pattern in which stress-inducing and non-stress inducing images are differentially responded to within those populations (Lang, 1995). However, it failed to demonstrate differential effects of childhood trauma, which contradicts the accumulated studies with a commonly used psychosocial stressor of the TSST showing a clear difference of hypo- and hyper-cortisol reactivity (Carpenter et al., 2007; Carpenter et al., 2010; Heim et al., 2000). Indeed, it is possible that the TSST may act on a different level of the HPA axis from the current method of image exposure that demonstrated adrenocortical abnormality in both resilient and vulnerable

individuals. This methodological issue needs to be addressed by a further refined stress-inducing method with the effect on a clear target level of the HPA axis to verify hormonal resilience and vulnerability to depression.

The current results have, otherwise, given an important implication for the presence of a long term effect of childhood trauma on HPA axis functioning. Whilst HPA axis changes are not apparently related to vulnerability or resilience to depression, all individuals who have a history of childhood trauma may acquire similar hormonal dysregulation that may not be reversible. The blunted cortisol reactivity identified within abused individuals implicates an adrenocortical abnormality which may be the consequence of adrenocortical downregulation in response to excessive ACTH releases in early stress reactions. This adrenocortical abnormality was still found in the current sample populations of adults whose events of childhood trauma took place decades ago. This suggests a persistent expression of this functional abnormality that may continue to affect those individuals for life and remains a scar that could potentially act as a trigger for the development of depression at any life stage. Those individuals who remain healthy despite such hormonal damage from childhood trauma may thus be assumed to have considerable behavioural strengths that can outweigh the potential vulnerability conferred by these “endocrine scars”.

3.4. Resilience and vulnerability – facial emotion recognition

As described earlier, one of the factors identified in this study that may afford such strength is the maintenance of strong startle affective modulation. Another is the positive bias that was found in healthy individuals with a history of childhood trauma at the experimental measure of facial emotion recognition. The latter is particularly robust evidence when contrasted with the negative bias that was found in depressed individuals with the same history. Ability to recognise facial emotions is important to guide one’s behaviours through social interactions. Impairment of this ability is likely to lead to difficulties in interpersonal interactions, such as aggression towards and conflicts with others due to misunderstandings of others’ intentions and distorted perceptions of situations. Such maladaptive behaviours can lead to intense or repeated psychological effects that could then be both direct and indirect triggers to the subsequent

manifestation of depression (Farmer, 2002; Lewinsohn et al., 1994). It is, indeed, rather intuitive that resilient individuals have the ability to more correctly perceive positive emotion than negative emotions, as a protective factor. With this ability, they perceive others behaviours to be amicable. Then they may be more able to make close and harmonious relationships with others than those without. This leads to successful management of supportive psychological environments and healthy mental wellbeing that prevents their manifestations of psychopathology. (Rosenblum, 2003)

A strong schema of positive facial expression, implicated for this superior ability to recognise positive emotions, may be shaped by experiences. The current results indicate that, while equally exposed to the adverse environments of childhood trauma, some individuals seem to be predisposed to attend more to positive emotions than others. Tendencies to attend to positive emotions thus facilitate a positive facial template within those individuals' mind to assist them to identify positive facial emotions more correctly and faster than other emotions. Superior affective modulation indicating greater responsiveness to different emotional contexts shown in healthy individuals with a history of childhood trauma may be associated with this process of shaping the positive schema. Sensitivity to emotional contexts that enables one flexibly to respond to different emotions is crucial for recognising emotional environments. Such sensitivity reflected in normal affective modulation may indirectly contribute to shaping the ability to efficiently capture positive emotions in the surroundings and then to protect individuals against the negative bias.

3.5. Neurofunctional consideration on the discrepancy between cognitive and hormonal stress reactivity

Taken together, the current project demonstrated individual differences in resilience and vulnerability to depression as a function of childhood trauma at different levels of neurocognition. At hormonal levels, both healthy and depressed individuals with a history of childhood trauma showed a similar cortisol dysregulation that may derive from adrenocortical abnormality. At behavioural levels, healthy individuals with a history of childhood trauma demonstrated their superior affective modulation and positive bias to facial emotions as cognitive resilience compared to depressed

individuals with a history of childhood trauma. The patterns of resilience and vulnerability were, however, not correlated between these levels. While a clear difference between resilience and vulnerability was observed at the behavioural levels, no such difference was found at the hormonal levels.

A possible explanation for this is considered based on the knowledge of the neurofunctional architecture of emotional responses to stress. The neural correlate of emotional processing is known to be located within the interactive circuitry of subcortical structures, including the amygdala and striatum, and the prefrontal cortex. Reciprocal interactions between these cortical and subcortical structures are involved in the generation and regulation of emotion (Ochsner and Gross, 2005; Ray and Zald, 2012). The amygdala, which is a phylogenetically old structure, subserves innate fight-flight responses that are prerequisite to human survival (LeDoux, 1996). Startles are part of this bodily fear responses and the amygdala is a main operation centre of startle activations (Davis, 1998). The prefrontal cortex, on the other hand, is the most newly developed brain area, and involved in modulating emotion-regulated signals from subcortical structures (Kalin et al., 2007). Attention, inhibitory control and interpretation of emotional signals are thought to engage the prefrontal cortex. This cortical control over amygdala responses is thought to play an important role to regulate emotion.

Inability to flexibly shift conscious attention to different emotional contexts may reflect dysfunction of this cortical control. Strong conscious attention to negative stimuli may override affective startle modulation, which is explained in the loss of balance in the interactions between these cortical and subcortical structures. Cortical regions are considered to have the ability to downregulate amygdala activity during emotion regulation (Diekhof et al., 2011). Attenuation of automatic responses of negative startle potentiation in depression thus is explained as cortical regions involved in strong attentional orientation to negative stimuli suppressing the amygdala involved in automatic emotion regulation of affective modulation. There is some support for this dysfunctional cortical-subcortical interaction from neuroimaging evidence showing greater cortical activation in depressed individuals in response to emotional stimuli (Kumari et al., 2003; Mayberg et al., 2000)

These cortico-limbic interactions, in contrast, are highly functional in healthy individuals with a history of childhood trauma, demonstrating their preserved affective startle modulation. Prolonged early stressful environments are found to be associated with the volume of amygdala in infants (Tottenham et al., 2010) and increased activation of amygdala in adults (Dannlowski et al., 2012), suggesting persistent amygdala dysfunction of emotion regulation for those who experienced childhood trauma. However, as the role of the prefrontal cortex becomes more dominant as age increases, cortical function replaces amygdala function for control over emotion regulation. Neurodevelopmental patterns of the prefrontal cortex have been identified in a shift from greater subcortical processing to greater cortical processing, thus suggesting greater interaction between subcortical and cortical structures (Casey et al., 1995). Preserved affective modulation found in the current sample of healthy abused individuals may thus be acquired through development as interactive cortical-subcortical circuitry matures and improves. The key cognitive strength that renders abused individuals resilient to depression may lie not solely in the cortical function per se but in successful integrity of connections between cortical and subcortical structures.

The HPA axis functioning of cortisol reactivity to stress may, however, not correlate with this cortico-limbic integrity. The activity of some prefrontal areas such as the orbitofrontal cortex and anterior cingulate cortex (ACC) has been found to be decreased in response to stress but not relate to cortisol activity (Pruessner et al., 2008). This may explain the absence of relationships between the current startle and cortisol measure as the ACC has been particularly known to subserve attentional control (Crottaz-Herbette and Menon, 2006; Posner and Dehaene, 1994). The current startle measure that heavily depends upon an individual's ability to control attention to emotional valence may have recruited such brain areas whose function may be distinct from the HPA axis functioning. Many imaging studies also report structural and functional alterations in these areas of the ACC, suggesting cortico-limbic dysfunction linked to childhood trauma (Hart and Rubia, 2012).

3.6. Therapeutic implications

This functional anatomy that possibly underlies cognitive resilience and vulnerability to depression, however, provides strong support for the advantage of the modification of attentional bias as one of therapeutic methodologies on a particular patient population with a history of childhood trauma. While hormonal dysregulation remains as a scar that is no longer reversible after development, emotional bias can be corrected even long after the childhood trauma occurred as the neuroplasticity in cortical areas that subserve this function endures into adulthood (Park and Reuter-Lorenz, 2009). A number of cognitive training task studies that aimed to modulate attention to emotional stimuli have been conducted and have shown some positive effects of ameliorating the negative bias in patients with psychiatric disorders such as depression and anxiety (Browning et al., 2010). In fact, there is evidence that psychological therapies are more effective in treating depressed patients with a history of childhood trauma than are pharmacological therapies (Nemeroff et al., 2003). As the attentional bias is a key functionality to explain the vulnerability to depression for this particular patient population, specially tailored therapeutic methods that target their attentional control mechanisms need to be explored. However, it is important to note that the interventions to alter attentional control mechanisms should be designed to consider individual differences of the preference of attentional directions to emotional valence but not of the efficacy of the system. For example, the activity of the ACC was decreased in negative but increased in positive situations in depressed patients (Knutson et al., 2008). The amygdala also activates differentially for positive and negative stimuli depending on certain personality traits (Canli et al., 2002). Efficient filtering of irrelevant negative information with improvement of working memory capacity also helps divert attention more towards positive directions. Successful application of cognitive training aiming for such improvement to depression supports their efficacy as possible interventions to alleviate depressive symptoms (Owens et al., 2013). Thus effective interventions should not aim simply to strengthen the cortical control over attentional systems but to alter the preference of directions of attention more towards positive emotional contexts by effectively employing the integrity of cortico-limbic function and executive function. The efficacy of this possible intervention of attention modification is also supported by psychotherapeutic model of post-traumatic growth. Instead of acquiring a negative bias as a consequence of the trauma, indeed, some individuals show positive changes following the trauma. For example, enhanced relationships, gains of wisdom and strength, and life philosophy in which they are encouraged to re-evaluate and appreciate

the meanings of life at aftermath of trauma, are included as factors of positive benefits they acquired through the trauma (Tedeschi and Calhoun, 1996) Post-traumatic growth is reported within the individuals who experienced traumas such as warfare, accidents, bereavements, disasters and life-threatening illnesses (Joseph, 2010). Psychological interventions are then designed to aim to facilitate positive psychology shown in this post-traumatic growth and to alleviate a negative bias. Psychological factors such as autonomy, environmental mastery, openness to personal growth, purpose in life and self-acceptance are among their specific therapeutic targets (Ryff and Singer, 1996). Personality factors such as emotional stability, extraversion, openness to experience, optimism and self-esteem also interact to facilitate greater post-traumatic growth. Coping styles including acceptance, positive reframing, seeking social supports, turning to religion and problem solving are factors that enable individuals to grow as a person at aftermath of trauma and improve their psychological capacity (Linley and Joseph, 2004). A person- centred approach in psychological therapy that aims to facilitate post-traumatic growth may therefore be one of the potential candidates that can be applied to specific patient populations with childhood trauma to promote their resilience and to modify their negative bias. Personality traits such as extraversion and conscientiousness that may be reflected on positive attitudes towards life were, in fact, found to correlate with resilience (Campbell-Sills et al., 2006). Unfortunately, to date, there is no research evidence to empirically demonstrate individual differences in the pathways to post-traumatic growth after the experiences of childhood trauma, and the field of research mainly focuses on the process of the recovery from physical illnesses. Nevertheless another interesting therapeutic possibility based on the theoretical model of post-traumatic growth is considered here in addition to cognitive resilience found in the current study. Despite the damaging effect of early life stress, efforts to implement cognitive modification and positive psychology are therefore hoped to deliver resilience to depression to the populations with a potential risk of manifesting adult depression.

3.7. Final conclusion – brain-behaviour relationship

In conclusion, the current study identified cognitive resilience, which is an attentional mechanism that allows individuals flexibly to respond to different emotional valence, within the healthy individuals with a history of childhood trauma. This resilience,

however, is distinct from the HPA functioning whose abnormality did not differentiate between resilient and vulnerable individuals in the current study. A straightforward brain-behaviour relationship for the effect of childhood trauma was not therefore found, at least at a one-to-one corresponding manner, when comparing resilience and vulnerability to depression between their psychophysiology and neuroendocrinology.

However, there are potential brain-behaviour relationships that can be inferred for the possible neuroanatomical functionality that underlies the expression of cognitive behaviours shown in startle and facial emotion recognition measures as outlined. A dissociation between the neural mechanisms of emotional processing on one hand and hormonal stress reactivity on the other is compatible with what is known about normal emotional regulation mechanisms.

As for a possible therapeutic implication, the underlying functional neuroanatomy suggests the advantage of cortical control over attentional mechanism as a cognitive resilience factor, with the hope that this could be implemented by attentional training to modify the negative bias specific to abused depressed patients. Hormonal dysregulation may be sustained throughout life but attentional flexibility might be improved by cognitive training and compensates for hormonal disadvantages of abused individuals.

3.8. Limitations

Limitations are also acknowledged in the three experimental measures used in the current study. Those are listed in the individual experimental chapters discussing the results from these measures.

Firstly antidepressant effects, which could not be eliminated in the current patient samples, may have compromised the effect of anxiety on the startle results. However, anxiety has been consistently found to enhance startle responses equally across all emotions (Grillon et al., 1998; Kumari et al., 2001). Strong normal affective modulation based on differential responses to different emotional contexts shown in abused healthy individuals should therefore be observed even if the level of anxiety differentially affects their overall startle magnitudes. Antidepressant effects should thus not be a

critical confounding factor for the main finding of affective modulation as cognitive resilience.

Secondly, methodological difficulties in the assessment of functional alterations at a specific level of the HPA axis were noted in the current passive image viewing paradigm. The current results were not entirely consistent with the previous results obtained using the most commonly used psychological stress paradigm, the TSST, and it is suggested that these methods may affect stress reactivity in different manners. In order to clarify this further, explorations of diverse stress-inducing paradigms administered concurrently in the same patients are warranted.

Thirdly, there is a possibility that an order effect in the three experimental measures conducted at the same day for each participant may have confounded the results. Towards the end of the experimental sessions with the duration of approximately two and a half hours, some participants, particularly the patients, were becoming mentally exhausted. Therefore, they may not have been able to perform the last task of facial emotion recognition with their best ability. This may be a possible reason why a significant mediatory effect of facial emotion recognition between childhood trauma and depression was not found.

The current study design employing healthy and depressed individuals with and without a history of childhood trauma also contains a number of limitations. For example, age ranges were not completely matched within the current sample groups. However, there were no significant age differences in these groups and the ages had no effects on the results when entered as a covariate in the analyses.

The use of samples which retrospectively report their experiences of childhood trauma also presents some difficulties in interpretation of the results. Retrospective reports are commonly criticised as unreliable as it is vulnerable to a memory bias. Experiences of childhood trauma can be both under- and over-reported. However, the CTQ, which was used to measure the experiences in the current study, is a standard battery and has been widely used in different empirical settings. In addition, those studies show consistent results in differentiating between abused and non-abused samples, as the current study also did (Carpenter et al., 2007; Carpenter et al., 2010).

The interpretation of the current study is also based on the assumption that cognitive resilience and vulnerability to depression were acquired through the experiences of childhood trauma. Genetic variance was not considered in the current study. Therefore, the possibility that an individual may actually be genetically predisposed for different depressive susceptibilities is not ruled out. Accumulated genetic studies in relation to childhood trauma suggest stress-diathesis models advocating the interactive effect of particular risk genes and environmental factors of childhood trauma on the diagnoses of depression. A number of genes are found to express vulnerability to depression only in the cases where the individuals carrying those genes were exposed to early life stress (Caspi et al., 2003; Heim et al., 2009; Kaufman et al., 2004; Ritchie et al., 2009). It is therefore possible that the current results of cognitive resilience and vulnerability may be the expression of these genes as a consequence of their interactions with the environmental factor of early life stress.

In addition, the period and lengths of childhood trauma which may critically influence functional mechanisms to confer individual differences of depressive susceptibility (Baker et al., 2013) are not analysed in the retrospective reports of traumatic incidents used in the current study. Future prospective studies tracing forward the development of cognitive resilience and vulnerability to depression after the incidents of childhood trauma combined with gene analyses are warranted for its clarifications of developmental pathways.

3.9. Final comments

Overall, the current study provides important new insights into the developmental pathways through which childhood trauma may predispose to adult depression, contrasting factors associated with functional resilience and vulnerability to depression. In addition, it has given an important therapeutic implication for a potential new treatment approach which can be specifically effective for the patient population with a history of childhood trauma. It is the first study in which the effect of childhood trauma was considered from multiple perspectives, combining the different research fields of neuroendocrinology, psychophysiology and behavioural psychology, with an attempt to

identify the underlying brain-behaviour relationship between all of these and the developmental route from childhood trauma to adult depression.

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Appendix

Appendix 1.

Medication type	Medication	Number
SSRI	Citalopram	2
	Escitalopram	3
	Sertraline	2
Tricyclic	Clompiramine	3
	Dosulepin	1
Other antidepressants	Duloxetine	3
	Mirtazapine	3
	Reboxetine	1
	Tryptophan	1
	Venlafaxine	9
Antipsychotic	Aripiprazole	3
	Clozapine	2
	Olanzapine	1
	Quetiapine	5
	Risperidone	1
Antimanic	Carbamazapine	1
	Depakote	1
	Lithium	6
Anxiolytic	Buspirone	1
	Diazepam	1

Table: List of the current use of anti-depressants in the depressed participants.

Appendix 2.

1)  2) 

3)  4) 

Examples of the images used for Experiment 1. 1) Positive image 2) Neutral image 3) Negative image 4) Childhood trauma-related image

Appendix 3.

For RT, there was a significant effect of emotion type (F (3, 201) =46.03 p<.001,) but there were no further main effects or two-way/three-way interactions. Post-hoc analyses revealed that happy RT (p<.001 with sad RT, fear RT and angry RT) was lower than all other emotions suggesting happy faces were the most efficiently recognised across the groups.

For ER, there was a significant effect of emotion type (F (3, 201) = 58.44 p<.001) but there were no further main effects or two-way interactions. A post-hoc analysis showed happy face ER was significantly lower than all other emotion ERs (p<.001 with sad ER, fear ER, angry ER), suggesting happy faces were most accurately recognized of all emotions across the groups. There was also a significant three way interaction (F (3, 201) = 2.91 p<.05) on ER. As is shown in Figures 2.3.1 and 2.3.2., happy ER was lower but all other negative ERs were higher in H/A than H/NA but an opposite pattern was found between D/A and D/NA. This three-way interaction remained significant even when all the scores of the current psychological and psychiatric assessments and age were entered as covariates (F (3, 180) = 2.92, p < .05). Post-hoc analyses of two-way ANOVAs on all emotion types revealed only a moderate interaction between condition and childhood trauma on happy ER (F (3, 67) = 3.54, p = 0.64 but not on other emotion ERs. The mean differences on happy ER were, therefore, the strongest component composing the significant three-way interaction on ER. .

For MB, there was a significant effect of emotion type ($F(3, 204) = 23.85$ $p<.001$) but there were no further main effects or two-way/three-way interactions. Post-hoc analyses revealed fearful face MB was significantly higher than all other emotion MBs ($p<.001$ with happy MB and sad MB; $p<.01$ with angry MB) suggesting fearful faces were the most misattributed of all emotions across the groups.

In analyses of the effect of the trauma type, there were no significant correlations with any of the emotional processing variables in D/A. However, a number of significant correlations were found between the CTQ subtype scores or CT number and the four outcome variables in C/A.

Emotional abuse was significantly positively correlated with fear RT ($r = .54$, $DF = 13$, $p <.05$) and fear ER ($r = .54$, $DF = 13$, $p <.05$). Physical abuse was significantly positively correlated with fear RT ($r = .54$, $DF = 13$, $p <.01$) and fear ER ($r = .61$, $DF = 13$, $p < .05$) and was moderately positively correlated with angry RT ($r = .69$, $p < .052$). CT number was significantly positively correlated with fear RT ($r = .75$, $DF = 14$, $p < .01$), angry RT ($r = .56$, $DF = 13$, $p <.05$) and fear ER ($r = .52$, $DF = 13$, $p < .05$). No correlations were found with sexual abuse, emotional neglect and physical neglect in C/A group.

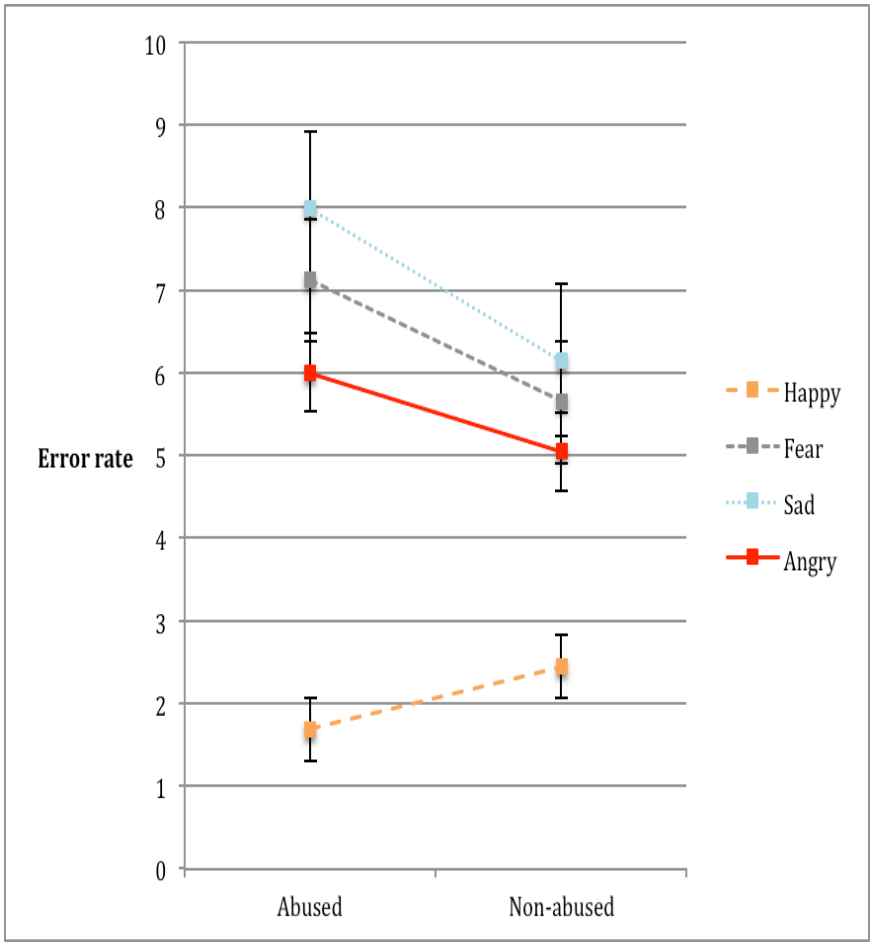

Figure 2.3.1 Mean ER with +/- 1 standard error for the four emotion types in healthy participants (abused/non-abused).

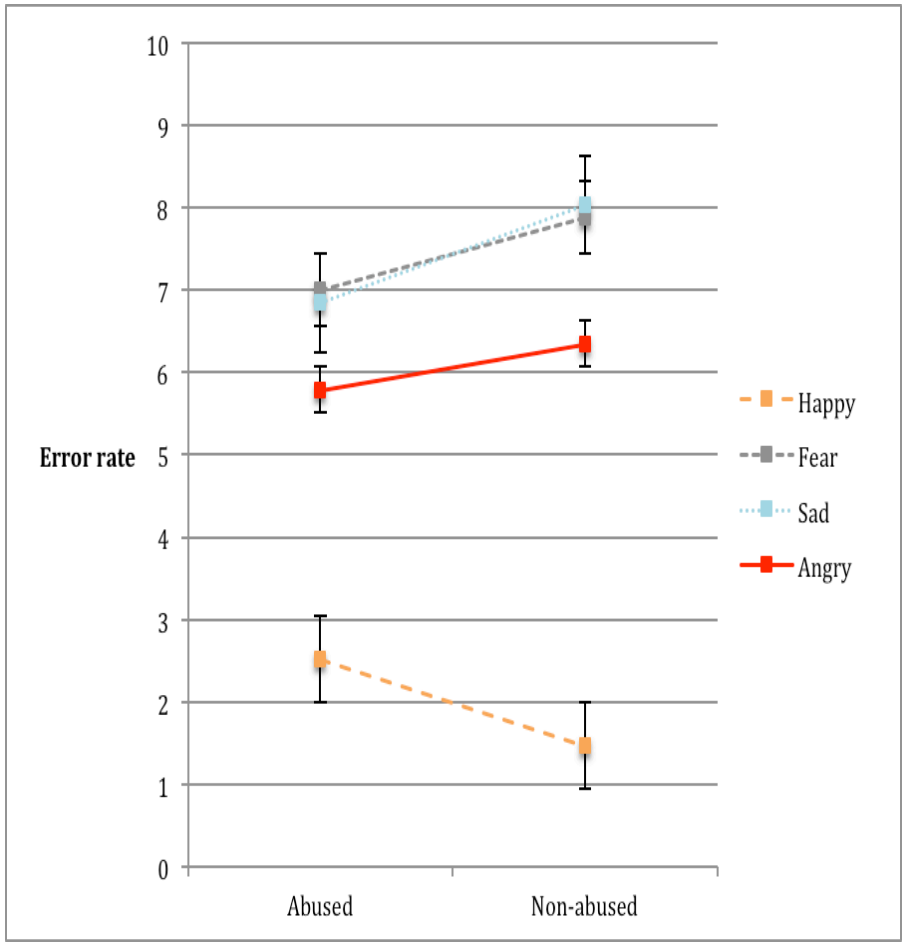

Figure 2.3.2. Mean ER with +/-1 standard error for the four emotion types in depressed patients (abused/non-abused).